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Understanding Optimum Fluoride Intake from Population-Level Evidence

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Abstract

Policy on fluoride intake involves balancing caries against dental fluorosis in populations. The origin of this balance lies with Dean's research on fluoride concentration in water supplies, caries, and fluorosis. Dean identified cut points in the Index of Dental Fluorosis of 0.4 and 0.6 as critical. These equate to 1.3 and 1.6 mg fluoride (F)/L. However, 1.0 mg F/L, initially called a permissible level, was adopted for fluoridation programs. McClure, in 1943, derived an "optimum" fluoride intake based on this permissible concentration. It was not until 1944 that Dean referred to this concentration as the "optimal" concentration. These were critical steps that have informed health authorities through to today. Several countries have derived toxicological estimates of an adequate and an upper level of intake of fluoride as an important nutrient. The US Institute of Medicine (IOM) in 1997 estimated an Adequate Intake (AI) of 0.05 mg F/kg bodyweight (bw)/d and a Tolerable Upper Intake Level (UL) of 0.10 mg F/kg bw/d. These have been widely promulgated. However, a conundrum has existed with estimates of actual fluoride intake that exceed the UL without the expected adverse fluorosis effects being observed. Both the AI and UL need review. Fluoride intake at an individual level should be interpreted to inform more nuanced guidelines for individual behavior. An "optimum" intake should be based on community perceptions of caries and fluorosis, while the ultimate test for fluoride intake is monitoring caries and fluorosis in populations.

Keywords: dental caries, dental fluorosis, oral health, public policy, risk-benefit balance, nutrient reference values

Introduction

Fluoride is the cornerstone of much of our efforts to prevent caries in child and adult populations. Some 75 y ago, dental researchers first established the dose-response link between the fluoride concentration in water supplies and the prevalence and severity of child caries and dental fluorosis (hereafter fluorosis) in populations. The research informed public health policy on the alteration of the fluoride content of water supplies to achieve a specific oral health outcome—the near maximal prevention of caries without an accompanying occurrence of fluorosis of public health concern. A benchmark fluoride concentration was adopted for implementation of water fluoridation policy in a temperate climate. Accompanying research estimated the fluoride intake in drinking water and foods associated with a water supply at the benchmark concentration. This was recommended for consideration as the "optimum" fluoride intake (McClure 1943).

While widely promulgated, the quantitative origins of an optimum intake have largely remained obscure and only occasionally been tested for their robustness. Burt (1992) referred to the unclear genesis of benchmarks for fluoride intake. Such benchmarks, however, have been crucial for high-level consideration of fluoride intake, helping define a deficient, adequate, and upper level of intake for populations and set policy and practice around the use of fluorides.

The aim of this critical review is to explore the origins and issues involved with key benchmark estimates of fluoride concentration in water supplies and fluoride intake.

Several premises underpin this review. First, while both population- and individual-level data can inform us about fluoride intake, policy on fluoride intake is intended to guide a population. Such guidance frames the likely intake of individuals, but it is not realistic for individuals to monitor or control their own fluoride intake. Second, while drinking water is the vehicle for which most of the historical research on fluoride, caries, and dental fluorosis is based, most of the underlying issues are relevant to other fluoride vehicles whether they be fluoridated salt, milk, toothpaste, or other oral health products like mouth rinses. All fluoride vehicles are ingestible, all can be absorbed, and all can contribute to chronic fluoride intake and hence both caries prevention and the occurrence of dental fluorosis either knowingly or unintentionally. This carries no weight in any inference about the mechanisms of action of

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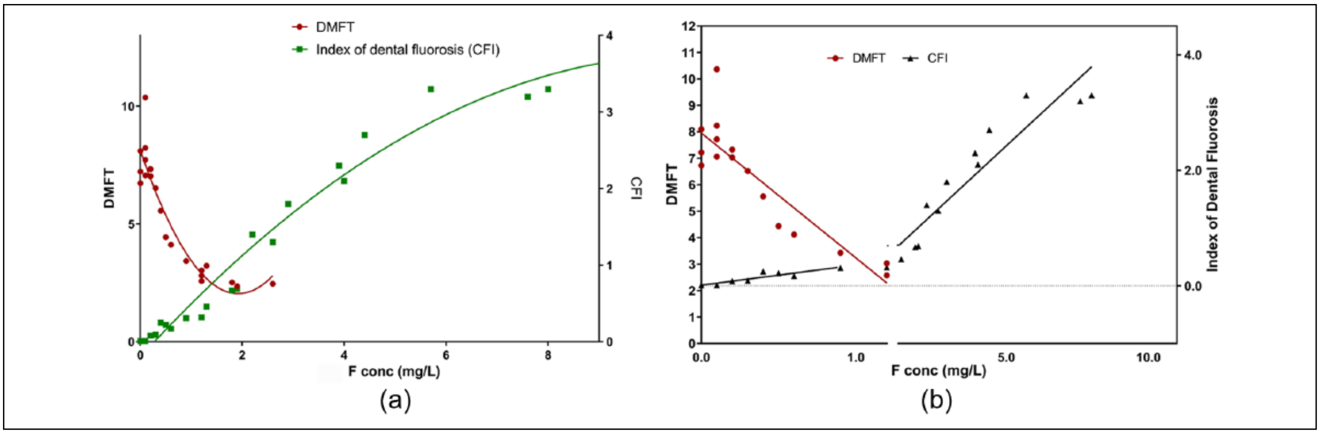

Figure 1. Dean's reported relationship between fluoride concentration, dental caries, and fluorosis. (**a**) Relationship between fluoride concentration, dental caries measured by mean decayed, missing, and filled permanent teeth (DMFT) score, and dental fluorosis measured by Index of Dental Fluorosis. Source: Dean (1942), 22 cities with fluorosis data; Dean et al. (1942), 21 cities with caries data. Lines of best fit were generated with a second-order polynomial (quadratic) equation. (**b**) Relationship between fluoride concentration on a log scale, dental caries measured by mean DMFT score, and dental fluorosis measured by Index of Dental Fluorosis—split at 1.05 mg fluoride (F)/L. After Hodge (1950). Source: Dean (1942), 22 cities with fluorosis data; Dean et al. (1942), 21 cities with caries data. CFI, Community Fluorosis Index.

fluoride. Just as it is argued that all fluoride vehicles can be ingested, it can also be argued that they all have some capacity to affect the caries mechanism at the tooth surface and/or via their ingestion and availability in the circulatory system during tooth development. It is the latter availability that also carries the risk of occurrence of fluorosis.

Fluoride, Caries, and Fluorosis: An Intimately Entangled Web

The research of Dean and others in the 1930s and early 1940s was initially focused on fluoride and dental fluorosis (Dean et al. 1935; Dean and Elvove 1935, 1936, 1937; Dean 1936, 1938) and then somewhat latterly turned to fluoride and caries (Dean et al. 1941, 1942). A "dose-response" relationship between fluoride concentration in water supplies and dental fluorosis was established in 22 cities in 10 US states[1] (Dean 1942). A "dose-response" relationship between fluoride concentration in water supplies and caries was established in 21 cities in and around Chicago and a further 4 states in the United States[2] (Dean et al. 1942; Dean 1946). Most, but not all, of the cities were common to both separate lines of research.

Dean was a pioneering population oral health researcher, an epidemiologist. Dean described epidemiology as "distinctly opposed to the clinical method in which the individual, rather than a population of individuals, is the unit of investigation. In an epidemiological inquiry, all observations are related to the group" (Dean 1942, p. 23). Dean pursued his research in the general population, filtered by certain exclusions that reflect an appreciation of the risk of misclassification of exposure across earlier years in children's lives. He understood the challenge of bias. "The physiological effects of previous fluoride ingestion—as indicated by the permanent teeth—may be measured by relatively precise quantitative means in large and comparable population groups differing only in the fluoride concentrations of their respective domestic water supplies" (Dean 1942, p. 24).

The relationship between fluoride concentration in a water supply by dental fluorosis has been presented as a positive association with the Index of Dental Fluorosis[3] and a negative curvilinear association with caries experience of permanent teeth expressed as the decayed, missing, and filled permanent teeth count (DMFT) (Fig. 1a). This relationship can also be presented by log transformation for the fluoride concentration and splitting of the linear relationship with the Index of Dental Fluorosis at 1.05 mg fluoride (F)/L (Fig. 1b). Such a figure has an intersection of the relationships at or around 1.0 mg F/L and implies that this point is important in a balance of prevention of caries with little occurrence of fluorosis. This oversimplifies that relationship between fluoride concentration in water supplies, caries, and fluorosis and only provides a post hoc pictorial rationale for the judgment on the balance of caries prevention and occurrence of dental fluorosis.

Dean had a considerable amount of additional data on these relationships. These additional data emphasize a more complex situation and the extensive overlap between the measures of the 2 conditions across the range of fluoride concentrations. This additional information challenges the simplified picture of the balance between the prevention of caries and the occurrence of fluorosis.

There is variance in the severity of fluorosis hidden behind point estimates of the Index of Dental Fluorosis. This can be seen in the relationship between fluoride concentration and the distribution of children by the severity of fluorosis (classified by the severest form of dental fluorosis recorded for 2 or more teeth in a child) (Fig. 2). Where there is a negligible fluoride concentration in water supplies, there is close to no occurrence of fluorosis. The occurrence of fluorosis is initially of questionable, then very mild or mild severity as fluoride concentrations increase. Only at higher fluoride concentrations is moderate or severe fluorosis seen.

The issue of variance around the point estimate for caries experience of permanent teeth expressed as DMFT can only be speculated. Unlike dental fluorosis, the distribution of DMFT

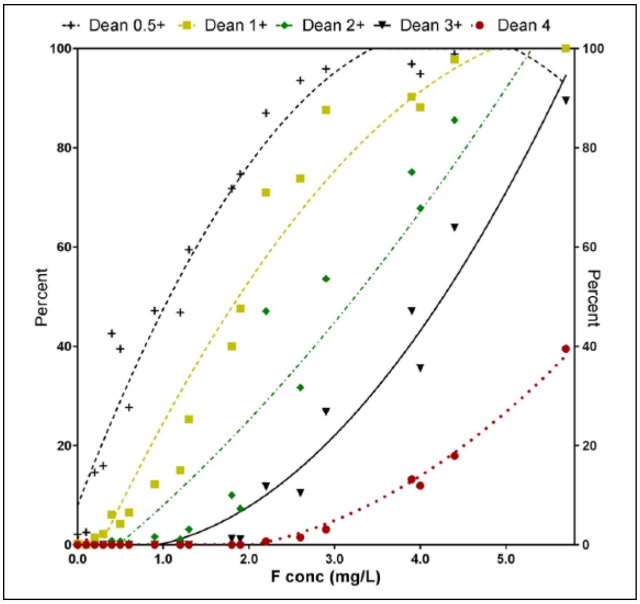

Figure 2. Relationship between fluoride concentration and the distribution of dental fluorosis scored by Dean's Index of Dental Fluorosis (0.5, 1, 2, 3, 4). Source: Dean (1942), 22 cities with fluorosis data. Lines of best fit were generated with a second-order polynomial (quadratic) equation.

scores is not given. However, some indication of this variance can be had by considering all 4 measures of caries experience that are available for the 21-city study. The 4 caries measures (percentage caries free, overall DMFT, upper incisor proximal surface caries, and first molar mortality) give some indication of the distribution of children with no caries experience through to those with "high" caries experience associated with upper incisor proximal caries and extraction of first permanent molars by age 12 to 14 y. These additional measures of caries foreshadow a more complex algorithm in estimating the benefit of fluoride concentration in the water supply than using DMFT alone.

Table 1. Dean's Differentiation between Index of Dental Fluorosis Scores in Terms of Their Importance.

Index of Dental Fluorosis	Descriptor	Importance
–0.4	Negative	Indices of little or no public health concern respecting the development of endemic dental fluorosis Highly important from standpoint of dental caries prevalence
0.4–0.6	Borderline	
0.6–1.0	Slight	Removal of excessive fluorides in water recommended
1.0–2.0	Medium	
2.0–3.0	Marked	
3.0–4.0	Very marked	

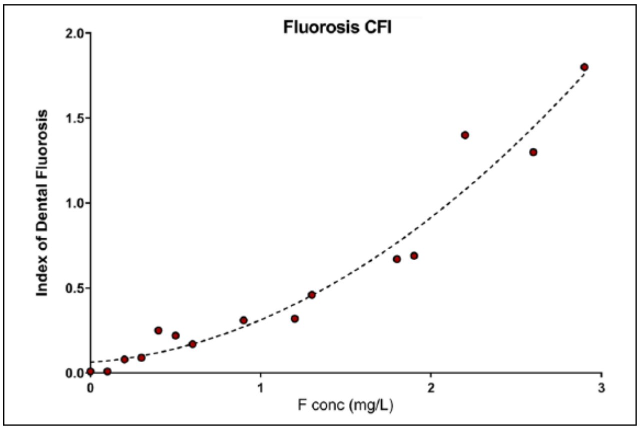

Figure 3. Relationship between fluoride concentration up to 2.9 mg fluoride (F)/L and dental fluorosis measured by the Index of Dental Fluorosis (or Community Fluorosis Index [CFI]). Source: Dean (1942), 15 cities with less than or equal to 2.9 mg F/L and associated fluorosis data. Lines of best fit were generated with a second-order polynomial (quadratic) equation.

An Optimal Fluoride Concentration in a Water Supply

The relationship between fluoride concentration in the water supply, caries experience, and fluorosis is far from straightforward. The complexity should alert us to the difficulty in arriving at judgments about "optimal" concentrations in a water supply. It is therefore informative to try to unravel the reasoning behind the identification of an optimal concentration.

Dean (1954), citing Dean (1942), clearly indicated that balance between caries prevention and avoidance of fluorosis of public health concern was guided by Index of Dental Fluorosis scores. These are presented in Table 1. Dean described Index of Dental Fluorosis scores of 0.0 to 0.4 and 0.4 to 0.6 of little or no public health concern in the development of fluorosis. This starting point has been recognized by others (Institute of Medicine [IOM] 1997; Verkerk 2010). The IOM (1997) indicates that the tipping point for judgment between caries prevention and occurrence of fluorosis of concern would equate to a fluoride concentration between 1.6 and 1.8 mg/L.

An analysis of the relationship is displayed in Figure 3. If the full range of fluoride concentrations available from the 22 cities in the United States is used, the relationship is curvilinear. However, if an equation is fitted to fluoride concentrations in the range 0 to 2.9 mg F/L, the relationship becomes near linear. This was also examined by Fejerskov et al. (1990) using Dean's data and was supported by data from Richards et al. (1967) and Butler et al. (1985) at low fluoride concentrations.

Interpolating from the fitted equation for Figure 3, the cut point for an Index of Dental Fluorosis score of 0.4 is 1.3 mg F/L. The city with a fluoride concentration closest to this in the Dean study was Joliet, Illinois (1.3 mg F/L), where the Index of Fluorosis was 0.37 and the prevalence of fluorosis (Dean's 1+) was 25.3%. Some 40.5% of children in Joliet had "normal" enamel, 34.2% questionable, 22.2% very mild, and 3.1% mild, and no children had moderate or severe fluorosis (Dean 1942).[4] Interpolating from the fitted equation, the cut point for an Index of Dental Fluorosis score of 0.6 is 1.6 mg F/L. The city with a fluoride concentration closest to this concentration was

Elmhurst, Illinois, USA (1.8 mg F/L), with an Index of Dental Fluorosis at 0.67 where some 28.2% of children had normal enamel, 31.8% questionable, 30.0% very mild, 8.8% mild, and 1.2% moderate fluorosis (Dean 1942).

It is interesting to speculate why a fluoride concentration of 1.0 mg F/L was chosen as "optimal." Dean wrote in 1944, "There seemingly is little if any advantage gained in further caries reduction by using a water higher than about 1 part per million [part per million or mg/kg]. And, as this concentration is sufficiently low to eliminate the complicating problem of dental fluorosis the question of markedly reducing the dental caries incidence through low fluoridation of domestic water supply warrants thoughtful consideration" (Dean 1944, p. 141). Dean later went on to say that "a strikingly low prevalence, accompanied by no more than sporadic instances of the mildest type of fluorosis with no practical aesthetic significance, was found associated with a fluoride content in the neighbourhood of 1.0 part per million" (Dean 1954, p. 325).

Dean and colleagues were making a judgment that the additional benefit in caries reduction of a slightly higher fluoride concentration did not warrant a slightly greater Index of Dental Fluorosis. A cautious approach might explain why a fluoride concentration lower than those associated with the 0.4 to 0.6 borderline zone for the Index of Dental Fluorosis was chosen. However, the chosen "permissible" or later "optimal" fluoride concentration was even below the 1.3 mg F/L, at which the Index of Dental Fluorosis was less than 0.4.

Dean (1954) also uses slightly different language to describe the emergence of 1.0 mg F/L as the chosen concentration. Dean refers to the "minimal threshold for mottled enamel, 1.0 ppm of F" and to the "minimal threshold of endemic dental fluorosis (1.0 ppm of F)." This judgment moves away from citing the Index of Dental Fluorosis to some notional threshold in the distribution of dental fluorosis scores. However, from the distribution data, it is not obvious what the threshold could have been. It certainly was not no occurrence of dental fluorosis, for very mild or mild fluorosis occurs at or between 0.0 and 0.4 mg F/L.[5]

McClure (1943) describes 1.0 mg F/L as the "permissible" level, citing the US Public Health Service (PHS) Drinking Water Standards (Parran and Miller 1943; US Public Health Service 1943). The Drinking Water Standards make little reference to fluoride in drinking water and provide no background information to the permissible level. The reference made is to a concentration limit (1.0 mg F/L) that should not be exceeded, where other more suitable supplies were available. It might follow that in terms of drinking water standards, this fluoride concentration should not be exceeded if upwardly adjusting the fluoride concentration of a water supply. It is in this sense that the word *permissible* could have been used by McClure. What is not explained is the process by which the permissible concentration in terms of drinking water standards was determined. It would seem likely that there was an accommodation of a safety margin that influenced public health authorities at the time.

If Dean and colleagues had stuck to the original interpretation of the Index of Dental Fluorosis for the threshold of fluorosis of no public concern, the optimal fluoride concentration might well have been at least 1.3 mg F/L to remain under the Index of Dental Fluorosis score of 0.4 or even as high as 1.6 mg F/L if one extends into the borderline zone, 0.4 to 0.6, of the Index of Dental Fluorosis.

Moving from "Optimal" Fluoride Concentration to "Optimum" Fluoride Intake[6]

Fluoride is an important nutrient. Countries have pursued public health policy to adjust fluoride intake at the population level with the aim of preventing dental caries without causing unacceptable fluorosis (or any other adverse effects). It is considered desirable to have a fluoride intake that is sufficient to achieve near maximal prevention of caries without exceeding intakes that are associated with "unacceptable" levels of fluorosis.

Since the Dean studies do not provide any details on water or food consumption for the populations studied, an indirect approach has to be adopted to convert exposure to water supplies with known concentrations of fluoride to population estimates of fluoride intake from drinking water and food in the diet. McClure (1943) was the first to pursue this translation. McClure estimated the drinking water requirement of children based around a formula of 1 mL of drinking water consumption relative to calories of energy in the daily diet. Two different assumptions were made: one that drinking water consumption was estimated for 25% of the daily total energy requirement and another 33% of the daily total energy requirement. Energy allowances for children were based on standards set by the National Research Council in 1942. Hence, average fluoride intake from water was based on standards for energy requirements. McClure estimated total fluoride intake from drinking water and foods and converted this to mg F/kg bodyweight (bw)/d.

McClure stated that at 1.0 mg F/L in drinking water, fluoride intake "probably would rarely exceed 0.1 mg per kilogram of body weight. As a rule, this average would equal about 0.05 mg daily per kilogram of weight for children" (p. 368). This intake "appears instrumental in reducing dental caries to a great degree" (p. 368). He suggests that "serious thought can be given to the use of this 'optimum' quantity of supplemental fluorine in children's diets for the partial control of dental caries" (McClure 1943, p. 369).

The range in most of McClure's estimates, presented in Table 2, is quite wide. This is especially so for the fluoride intake from foods. The total daily fluoride intake range is wide because the extreme estimates of the fluoride intake from drinking water and food estimates are summed. In arriving at the 0.05 mg/kg bw/d, McClure seems to have taken the midpoint of the various ranges. How realistic it is to take the midpoint as an average is difficult to ascertain. It is produced under different assumptions that need to be tested. However, it should be noted that the midpoint is 0.065 mg F/kg bw/d for 1- to 3-y-olds and 0.05 mg F/kg bw/d for 4- to 6-y-olds.

It is difficult to have a lot of confidence in this estimation, yet it has had a profound influence. Among researchers, one

Table 2. Estimated Daily Fluoride Intakes with 1 mg F/L in Water with Dry Substances of Food (McClure 1943).

Age, y	Bodyweight, kg	Tap Water Consumption,[a] mL/d	Drinking Water, mg F/d	Food, mg F/d	Total F Intakes, mg F/d	Total Daily F Intakes, mg F/kg bw
1–3	8–16	300–396	0.390–0.560	0.027–0.265	0.417–0.825	0.03–0.10
4–6	13–24	400–528	0.520–0.745	0.036–0.360	0.556–1.105	0.02–0.08
7–9	16–35	500–660	0.650–0.930	0.045–0.450	0.695–1.380	0.02–0.07

bw, bodyweight; F, fluoride.

[a] Range between 25% and 33% of total daily water requirement—estimated to be 1 mL per calorie of energy in the daily diet.

can find it variously referred to over many years. Farkas and Farkas (1974) cite others as recommending 0.06 mg F/kg bw/d would be an accepted fluoride intake, although McClure is not specifically cited. Ophaug et al. (1980) suggested that the range of 0.05 to 0.07 mg F/kg bw/d "is generally regarded as optimum." Burt (1992) concluded that despite its dubious genesis, 0.05 to 0.07 mg F/kg bw/d remains "a useful upper limit for fluoride intake in children" (p. 1230). While the estimates are all similar, the change in wording in these few quotes is crucial. Language shapes meaning.

Several points need to be acknowledged about this "optimal" fluoride intake. First, it does not seem to be tied to a specific outcome in the balance of the prevention of caries and occurrence of fluorosis. This leads to unfortunate consequences. For instance, Dean (1944, p. 141) predicted the reduction in caries that would be achieved in moving from negligible to optimal fluoride concentration in a water supply, but not the occurrence and distribution of fluorosis. Too often, it seems that optimal is interpreted as achieving the former without any of the latter being considered. Second, there is rather casual use of words like *optimal* in some of the earlier literature, but this then moves to an upper limit not to be exceeded.

Public Policy Consideration of Fluoride Intake

The fields of research that attempt to estimate the beneficial or adverse effect of intakes or exposures to micronutrients are toxicology and nutrition, hopefully informed by expertise in the specific micronutrient and its beneficial and adverse effects. Variously structured groups have developed advice to health authorities about estimates called "Nutrient Reference Values" (Australia and New Zealand) or "Dietary Reference Intakes" (United States). Fluoride is an important but nonessential nutrient. It is important to tooth development and in modulating the caries process in erupted teeth. It is also a nutrient that attracts considerable questioning of whether intakes are associated with beneficial or adverse effects. It is, therefore, not surprising that there is a growing list of investigations of intake of fluoride as a nutrient that are assessed against Nutrient Reference Values, for example, an Adequate Intake (AI) and Upper Level of Intake (UL) across a range of ages.

The first detailed report on Nutrient Reference Values for fluoride was produced by the Standing Committee on Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board (IOM 1997). The IOM report initially sets about rationalizing an AI for fluoride. An AI was defined as an intake that has been shown to reduce the occurrence of dental caries maximally in a population without causing unwanted side effects, including moderate dental fluorosis. The IOM accepted that populations served by water supplies with 1.0 mg F/L achieve a near maximal reduction of caries in a temperate climate without causing unwanted effects. The average dietary intake of fluoride in areas of the United States with fluoridated water supplies at around 1.0 mg F/L has been close to 0.05 mg F/kg bw/d since the 1980s. This estimate was largely driven by Ershow and Cantor (1989) data on water intake in the United States but was remarkably close to that of McClure (1943). The focus for policy needs to be on the ages up to 8 y. It is up to this age that the judgment about the balance in the prevention of caries and occurrence of fluorosis is sharpest. Intakes in older children will be relevant to the prevention of caries but not to the etiology of dental fluorosis. Conceivably for older ages, a different adverse end point might be considered such as skeletal fluorosis, which seems limited to much higher chronic fluoride intakes.

The second value estimated by the IOM was a Tolerable Upper Intake Level, referred to in this review as the UL. The UL is the highest level of nutrient intake likely to pose no adverse effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of the adverse effect increases. The IOM report identified moderate fluorosis using Dean's index (i.e., a Dean's index score of 3 as the threshold of fluorosis that was an adverse effect). Moderate and severe forms of fluorosis were judged as being aesthetically objectionable changes in tooth color and surface irregularities (loss of enamel and pitting). The most appropriate data available to the IOM to identify fluoride intakes associated with moderate fluorosis as an end point were Dean's data on the 22 cities in the United States. At the time of their data collection, the fluoride intake was almost exclusively from the diet (naturally occurring in drinking water and foods) and not affected by water fluoridation programs, intake from oral health products, or professional applications.

Dean's 22-city data were used to identify 2 key points in the fluoride concentration of water supplies that related to the occurrence of moderate fluorosis. These are the no observed adverse effect level (NOAEL) and the lowest observed adverse effect level (LOAEL). From Dean's data, the fluoride concentration in a city that informed the NOAEL was 1.9 mg F/L in Galesburg, Illinois (0% prevalence of moderate fluorosis), and for the LOAEL, it was 2.2 mg F/L in Clovis, New Mexico, USA (0.2% prevalence of fluorosis). The fluoride intake for a water supply with a concentration of 2.0 mg F/L was estimated. The fluoride intake of most children under 8 y of age in such a community ranged from 0.08 to 0.12 mg/kg/d. An average, daily fluoride intake of 0.10 mg F/kg bw/d was said to be the threshold beyond which moderate fluorosis appears in some children. There was little uncertainty between the fluoride intake and the adverse effect, so the uncertainty factor (which could lower the UL) was set at 1, or unity. A UL was then calculated for a range of ages based on bodyweight.

At a slightly earlier time to the IOM (1997) report, the Panel on Dietary Reference Values in Great Britain (Committee on Medical Aspects of Food Policy 1991) recommended 0.05 to 0.07 mg F/kg bw/d—the optimum range suggested by Ophaug et al. (1980)—without much discussion or argument. The lower estimate in the range is consistent with the IOM's estimated AI.

Subsequent reports have supported the IOM AI or UL values. The European Food Safety Authority (EFSA) (2005) reviewed the UL for fluoride intake. No UL was established for infants less than 1 y old. ULs for 1- to 3-y-olds and 4- to 8-y-olds were based on the threshold of 0.10 mg F/kg bodyweight/d. No estimate of an AI was presented. The European Union's Scientific Committee on Health and Environmental Risk (SCHER) in 2011 was requested to provide scientific opinion for new evidence on fluoride intake. No new evidence was identified to change the established values for UL published by EFSA in 2005. In 2013, EFSA assessed fluoride intake to provide advice on Dietary Reference Values for fluoride (EFSA 2013). EFSA in 2013 placed considerable weight on the beneficial effects of fluoride intake on caries. The conclusion was that, based on available scientific evidence, an AI for fluoride from all sources should be 0.05 mg F/kg bw/d for all children and adults. Thus, the threshold values of the IOM were adopted in estimating the AI and UL for fluoride. Other countries have also adopted the IOM threshold values, sometimes with little apparent further consideration. Australia's National Health and Medical Research Council (NHMRC) did so in 2005 (NHMRC 2006).

However, in 2010, the US Environmental Protection Agency (EPA), Office of Water revisited both the AI and UL for fluoride (EPA 2010a). No change was made to the IOM AI. It remained at 0.05 mg F/kg bw/d. However, they reanalyzed Dean's data for the fluoride concentration in relation to fluorosis. The US EPA changed the adverse end point to severe fluorosis and lowered the tolerable occurrence from 5% for moderate fluorosis to 0.5% for severe fluorosis. This was justified by a consensus that severe fluorosis is an adverse effect (basically because of aesthetic concern and the possibility of "imperfect" enamel being more susceptible to caries; National Research Council [NRC] 2006). The data available on severe fluorosis also better suited specific dose-response modeling used to estimate the Benchmark Dose (BMD; approximately equivalent to the LOAEL). The BMD was estimated to be 2.14 mg F/L, and the lower 95th confidence limit of the BMD, the BMDL (approximately equivalent to the NOAEL), was 1.87 mg F/L. The Reference Dose (RfD) was estimated by calculating the median (50th percentile) fluoride intake assuming drinking water at 1.9 mg F/L and fluoride intake from foods for several age groups. This initially produced an illogically low RfD (in relation to the AI), so the EPA adjusted the RfD upward, arriving at a final RfD of 0.08 mg F/kg bw/d.

Critique of the AI and UL Estimates

There are several issues to consider with the available estimates of an AL and UL. Although there has been a longstanding acceptance that the fluoride intake associated with drinking water at around 1.0 mg/L is a basis for an AI, this should not go unquestioned. The basis of the AI is the wide acceptance of a 1.0-mg F/L concentration of a water supply in a temperate climate as a benchmark and McClure's calculation of the fluoride intake among children consuming water at that concentration. It seems possible that this fluoride concentration is somewhat conservative. Dean's interpretation of the Index of Dental Fluorosis indicates that the normative judgment of this would indicate a fluoride concentration of around 1.3 mg F/L. Furthermore, there is a distinct possibility that McClure was cautious and that an estimate of fluoride intakes varying from 0.05 to 0.065 mg/kg bw/d or higher could have been determined. Acceptance of these issues would lead to a revised AI.

The epidemiological and toxicological basis of a UL is straightforward. The NOAEL of around 1.9 mg F/L from Dean's dose-response data seems well accepted. However, the next steps of the estimation of the fluoride intake associated with this fluoride concentration in drinking water are more open to challenge. At issue is the distribution of drinking water consumption and consequently fluoride intake estimates in a population with the NOAEL fluoride concentration in their water supply. Drinking water consumption is log normal in its distribution (Burmaster 1998). The mean is lower than the median, and there is about a 1.7-fold difference between the mean and the 95th percentile of drinking water intake (Ershow and Cantor 1989). Therefore, the crucial issue is whether a measure of central tendency (mean) or a certain percentile in the distribution is used to calculate the fluoride intake at the NOAEL.

The RfD (sometimes assumed to be the equivalent to the UL) for the EPA (2010a) was estimated as the fluoride intake associated with the mean drinking water consumption at the BMDL of 1.9 mg F/L. Yet, no child in a population drinking water with 1.9 mg F/L had the occurrence of severe fluorosis, the chosen end point. Therefore, it can be argued that when calculating the fluoride intake at the BMDL or the NOAEL, the 95th percentile of intake could be used.

If the basis of the calculation of an AI does not change (i.e., it is based on fluoride intake from drinking water at 1.0 mg F/L and foods), estimates will be close to 0.05 mg F/kg bw/d. However, if the basis of the calculation of an UL is a NOAEL of 1.9 mg F/L and fluoride intake is estimated for the 95th percentile of fluoride intake, then the UL will be closer to 0.2 mg F/kg bw/d. This is effectively double the previous widely quoted value by the IOM of 0.1 mg F/kg bw/d (NHMRC/MOH 2017).[7]

The Exceedance Conundrum

A considerable body of research documents fluoride intake for children in contemporary populations. Collectively, the research describes the fluoride intake from drinking water, all other beverages, foods, and tooth brushing with fluoridated toothpaste. In fluoridated areas, the relative source contributions are generally described for 1-y-olds as 70% drinking water with the bulk of the remainder as foods and for 1- to 3-y-olds as 40% drinking water, 20% beverages, 20% foods, and 20% toothpaste. Among 4- to 7-y-olds, the intake is again about 40% from drinking water, 15% foods, 20% beverages, and 10% toothpaste (EPA 2010b). However, there is great variation in the estimates of source contributions from one study to the next, particularly for toothpaste. Fluoride toothpaste ingestion has been reported as the majority contributor to fluoride intake in several studies (Franco et al. 2005; de Almeida et al. 2007; Zohoori et al. 2012).

What these data hide is the sensitivity to methods, the impact of key assumptions, and the resulting high interindividual variation and, might it be suggested, the high intraindividual variation in fluoride intake estimates. There is variation between those estimates theoretically based on standard diets, those based on food frequency questionnaires, those based on a diet diary, and those that have used a duplicate plate approach. Variation in the estimated intake from toothpaste is high, with some research using standard "serve" size and age-standardized estimates of toothpaste ingested (and fluoride intake), while others have used observational research to quantify the amount of toothpaste dispensed minus the amount of fluoride recovered in expectorated slurry. Then there are assumptions about the number of tooth brushings per day. Most estimates of fluoride intake are based on only 1 brushing a day, even though contemporary surveys document twice-a-day brushing as the most frequent pattern of use. No consideration is given to the licking or eating of toothpaste on fluoride intake despite reports of this being quite a common behavior (Riordan and Banks 1991; Spencer and Do 2007).

If one stays with the formal reports on Nutrient Reference Values for fluoride such as the IOM report, a high percentage of children at early ages in areas with drinking water at 1.0 mg F/L have a fluoride intake that exceeds the AI of 0.05 mg F/kg bw/d. This is hardly surprising given that the AI is estimated as the mean fluoride intake associated with drinking water with 1.0 mg F/L. Given the log-normal distribution of drinking water consumption, some 40% of children will have a fluoride intake that exceeds the AI. This sends a message about the interpretation of the AI.

Reasonable proportions of children in areas with drinking water at 1.0 mg F/L will have a fluoride intake that exceeds the IOM UL. Australian research as part of the consideration of the voluntary addition of fluoride to package (bottled) water found that 22% of 2- to 3-y-old children had a fluoride intake that exceeded 0.10 mg F/kg bw/d (Hambridge and Buffinton 2008; Food Standards Australia New Zealand [FSANZ] 2009). Yet, the occurrence of moderate or severe fluorosis is rare in epidemiological research in Australia and comparable countries.

This conundrum forces us to question the basis of the IOM UL. Revision of the UL through use of the 95th percentile estimated fluoride intakes would result in an UL approximately 4 times the IOM's AI and twice its UL. Actual estimates of daily fluoride intake may extend above the AI but will be well below a revised UL for children aged up to 8 y. A problem of individuals exceeding the fluoride intake at the AI (when this has been asserted to be an optimal fluoride intake) and/or UL is no longer inferred. The higher UL derived from the above logic would establish a considerable safety margin between the AI and UL, a margin into which many children's fluoride intake will fall (NHMRC/MOH 2017).

Water Consumption and Outside Air Temperature

The basis of the above considerations is fluoride intake estimated from drinking water consumption in a temperate climate, like that of Chicago, Illinois, USA. The importance of variation in water consumption to temperature was recognized by Maier (1950) and Galagan (1953). The relationship between water consumption and outside (or ambient) air temperature was established by Galagan and Vermillion (1957), who looked at the variation in water consumption of 0- to 10-y-olds measured over a 5-d period and different seasons across 2 different temperature zones in California. The relationship between water consumption and mean maximum daily temperature, which was subsequently proposed, was as follows:

$$\text{Water intake per bodyweight in ounces/pounds (oz/lb)} = -0.038 + 0.0062 \times \text{Mean maximum daily temperature.}$$

Using this equation with a fluoride concentration of 1.0 mg F/L for a temperate climate like Chicago with a mean maximum daily temperature of 61.6°F led to an adjustment formula for fluoride concentration levels (Adjusted F) for different climates of

$$\text{Adjusted F “optimum” fluoride concentration} = 0.34 / (-0.038 + 0.0062 \times \text{Mean maximum daily temperature [degrees Fahrenheit]}).$$

There have been several analyses of the relationship of water consumption and temperature since (Ershow and Cantor 1989; Heller et al. 1999; Sohn et al. 2001; Beltrán-Aguilar et al. 2015). It is possible that the type of data collected and analytic approach used in some of these studies may favor finding no strong relationship between temperature and drinking water consumption. Longer observation periods across the seasons and an analysis across populations and temperature zones might be more appropriate than short recall periods and individual-level analyses.

To the extent that temperature is associated with drinking water consumption and drinking water consumption is an important contributor to fluoride intake, any shift in the distribution of drinking water consumption should be factored into trying to achieve a specific fluoride intake, for example the AI, by adjusting the fluoride concentration of water supplies.

A complication arises from trends in water consumption over time. A decreasing proportion of drinking water consumption is contributed by tap water. There has been a substantial increase in soda (soft) drinks and bottled water consumption. The manufacturing of soda (soft) drinks has moved to use of distilled water, reducing the potential fluoride intake from drinking water. The fluoride content of bottled waters, while varied, is not infrequently low. A reduction in the contribution of tap water to total drinking water consumption could justify an increase in the fluoride concentration in drinking water supplies after any adjustment for temperature to achieve specific fluoride intakes.

Interindividual and Intraindividual Variation in Fluoride Intake

Variation in fluoride intake of children of a similar age in a similar community context is a striking feature of individual-level research on fluoride intake. Most notable among such research is the Iowa Fluoride Study. Levy and colleagues toiled across years to estimate fluoride intake initially at 3-mo, then 4-mo intervals until age 3 y, then 6-mo intervals (Hong et al. 2006; Levy et al. 2010). Warren et al. (2009) presented data on mean fluoride intake for 4 groups: those children with no caries, no fluorosis (using the Fluorosis Risk Index with at least 1 tooth with a score of 2 or 3), neither, or both. Mean estimates in mg F/kg bw/d were similarly patterned by age for all 4 groups. There was an expected but only modest (not significant) variation of fluoride intake by the occurrence of fluorosis only (slightly higher mean intake) and caries only (slightly lower mean intake). However, when the fluoride intake of those children at age 9 y with neither caries nor fluorosis was examined, there was a range of fluoride intakes from close to zero to well above 0.10 mg/kg bw/d. The Iowa Fluoride Study data emphasized the wide interindividual variation in fluoride intake and the importance of considering the distribution of intakes around any point estimate of fluoride concentration in a water supply chosen for the estimation of an AI or UL.

A further issue is the lack of certainty whether individual children with a higher or lower fluoride intake were consistently ranked over time in their relative position for fluoride intake. This adds another layer of variation, an intraindividual child variation across time. This complicates any interpretation, requiring both consideration of any absolute intake estimate and its specific timing across the developmental period. Levy and colleagues have explored some aspects of intake and timing but against the occurrence of *any* fluorosis. A further complication is that the relative source contribution to fluoride intake is changing for all children by age and will change within an individual child from one time point to another. Not all fluoride intake from different sources or across time may be as beneficial or adverse for caries and fluorosis.

The difficulty in interpreting individual-level fluoride intake data for the estimation of an AI and UL is an example of the search for associations within versus across populations. This is the situation initially described by Rose in his classic paper on sick individuals or sick populations (Rose 1985). McMichael has described this in rather colorful terms "oriented to explaining and quantifying the bobbing of corks on the surface waters, while largely disregarding the stronger undercurrents that determine where, on average, the cluster of corks ends up along the shoreline of risk" (McMichael 1995, p. 634). Dean recognized the variation within a population, commenting, "Among individuals of even an apparently homogeneous group there are natural differences in sensitivity (or resistance)" (Dean 1942, p. 29). A crucial element of Dean's original work is its focus across several populations with very different fluoride concentrations naturally occurring in the water supply.

Optimum Fluoride Intake

An emphasis so far has been the identification of key concentrations of fluoride in a water supply and the reasoning behind the calculation of fluoride intakes at the AI and UL. What needs further consideration is an optimum fluoride intake. Optimum fluoride intake should represent a desired balance between the prevention of caries and the occurrence of fluorosis.

Dean and colleagues initially made a judgment on the desired balance of caries and fluorosis associated with their reported dose-response relationships. Dean (1942) indicated the presence of fluorosis up to an Index of Dental Fluorosis of 0.4 or even 0.6 was acceptable given the highly important prevention of caries. This was a normative or professional judgment about the perceived impact or importance of the fluorosis observed in populations with a range of Index of Dental Fluorosis scores against the observed prevalence of caries.

The crucial issue here is the nature of the judgment. It is a judgment about what level of caries in a population and what level of fluorosis in a population produce an optimum level of oral health. It is the estimation of a production function for oral health, where oral health is a function of caries and fluorosis experienced. While it might be assumed that no caries and no fluorosis would be optimum oral health for an individual, that outcome is not observed for contemporary populations. Populations have a mix of these 2 conditions. The production of oral health becomes more complex when this question is framed as what level of caries and what level of fluorosis results in a maximum oral health for a population.

This is not a straightforward trade-off, that is, not a trade of a case of caries against one case of fluorosis. Using a self-reported "global" oral health measure, Do and Spencer (2007a) found that when children and their parents considered a child's situation, there was a linear decrease in oral health as caries experience in either dentition increased from zero to 1 to 2, 3 to 4, to 5+ teeth. However, there was no such linear increase in oral health as fluorosis severity decreased from a Tooth Fluorosis (TF) Index score of 3 to 2, 1, or 0. Children rated their own oral health of a TF score of 1 and 2 above that of a child with a TF of 0, while parents rated the oral health of a child with a TF score of 2 above that of a child with a TF score of 0. For both children and parents, a TF score of 3 was rated not significantly different from a child with a TF of 0.

However, there is a lack of independence between the oral health ratings of these 2 conditions. A lower caries experience was associated with a greater probability of fluorosis and a higher fluorosis score (Do et al. 2009). This trade-off was evident from multivariable logistic regression models of both child and parent ratings of oral health (Do and Spencer 2007a). For both caries experience in the presence of fluorosis and fluorosis score in the presence of caries, it was evident that the global rating of oral health deteriorated with increasing caries. The global rating of oral health was higher for TF scores 1, 2, and 3 than for TF 0, but for children, this was only significantly higher for TF 2 than TF 0. Among parents, the global rating for TF 1 and TF 2 was higher than TF 0, but TF 3 was lower than TF 0.

These results indicate some of the complexity of the judgment about the balance between benefit and adverse effect of fluoride intake. Other analytic techniques, most likely with other larger data sets, might shed more light on the judgment as made by children and parents in the community. One approach would be to map out the global rating of oral health (or oral health–related quality of life) for all possible combinations of pairs of scores for caries experience and fluorosis. It might seem sensible that no caries and no fluorosis (of any severity) is a key reference point. This is also the situation with a reasonable proportion of children in many high-income countries. However, while existing research (Do and Spencer 2007a) would indicate that a low experience of caries with no fluorosis would be associated with a lower rating of oral health than the reference, it is far less certain that a no caries but low severity of fluorosis will be rated as lower oral health than the reference of no caries or fluorosis. As one works through the combinations, it may be that for some, there is no significant difference against the reference, while others are significantly different. This could guide a reinterpretation of Dean's data on what was an "optimal" concentration of fluoride in a water supply and subsequently an optimum fluoride intake.

This underlying approach has been used in small-scale studies where people were asked about their perception of various oral health scenarios. This was the approach adopted by Nair et al. (2016). Interestingly, they found that the judgment on need to seek correction for a presenting situation showed that only severe fluorosis was assessed as requiring correction, but that easily visible caries was rated with a higher need for correction than severe dental fluorosis.

While this might seem complex enough, further issues need to be acknowledged. First, these 2 conditions have entirely different natural histories over the life course. Caries is a chronic accumulating disease with well-established sequelae, most of which are associated with destruction of hard tissues, infection, pain, and invasive treatments, which have associated discomfort and considerable cost. Dental fluorosis, at least at the level of severity without loss of enamel or pitting, is a developmental condition with a limited critical period of origin. Its consequences are of an aesthetic nature, and while more severe cases might be associated with psychological discomfort or even disability, that is by no means certain. There is also a growing body of research that comments on thresholds of fluorosis noticed by children or parents and whether different thresholds of fluorosis are perceived as affecting appearance (Chankanka et al. 2009).

The reliance of the York (McDonagh et al. 2000) and Cochrane (Iheozor-Ejiofor et al. 2015) reviews on a single study in Manchester, United Kingdom, to establish a threshold for an effect on appearance is useful but does not go far enough (Hawley et al. 1996). Hawley et al. (1996) had 14-y-old children rate the appearance of pictures of fluorosis with known TF Index scores. The cut point was taken as the level of fluorosis above which children classified the pictures as "very poor" or "poor" in appearance. In these 2 key reviews, this threshold with the TF Index was a score of 3 or more and was judged to be equivalent to a Dean's index score of mild or above and a Tooth Surface Index of Fluorosis (TSIF) score of 2 or more. An effect on appearance is a necessary but not a sufficient condition for fluorosis to affect ratings of "oral health." A rating or metric of "oral health" is required to establish optimum outcomes for caries and fluorosis in combination.

Community perception of what is adverse aesthetically can and has changed. Such a perception is a social construct that is being redefined over time. It is plausible that opacity associated with low-severity fluorosis is now interpreted as whiter and more desirable teeth. Treatments are available to mitigate variation in tooth whiteness and appearance associated with low-severity fluorosis. These were predominantly etching and abrasion, but tooth-whitening treatments can now be added. These are not as invasive or expensive as treatments for caries.

Second, the original research of Dean and colleagues and the recent research of Do and Spencer (2007a) were conducted with children up to 13 or 14 y old. There is a dearth of research to describe the natural history of dental fluorosis. When Do et al. (2016) conducted a follow-up of the participants in their research some 7 to 8 y later, 87% of individuals with an original TF score of 0 stayed at 0. Conversely, some 46% of individuals whose original fluorosis score was TF 1 had a follow-up score of TF 0, and 23% of those whose fluorosis score was TF 2 or 3 had a follow-up score of TF 0 and 32% a TF 1. It was apparent that there was a greater proportional shift downward to lower or even zero scores for fluorosis. These data have been interpreted as evidence of a diminishing of fluorosis with aging. Increasing knowledge of the ongoing enamel demineralization and remineralization processes and/or tooth enamel wear provides biological plausibility for these outcomes.

A Way Forward for Policy Formulation

It is important that oral health research contributes to guidance on fluoride intake. Estimates of an AI, optimum, and a UL for fluoride intake are important in framing policy on the use of fluorides for oral health. Some 25 countries have implemented fluoridation of their water supplies and a further 25 have implemented salt fluoridation (British Fluoridation Society 2016). A few additional countries have implemented milk fluoridation (Banoczy et al. 2009). It is argued that estimates are important even for populations that have no community water, salt, or milk fluoridation programs. Many populations have some naturally occurring fluoride either in tap water or in bottled mineral water. Fluoride intake will be shaped by a complex mix of all these potential fluoride vehicles. For instance, Belgium reportedly has about 40% of the population exposed to fluoridated salt (SCHER 2011), and further areas are identified as having fluoride occurring naturally in water supplies and in many natural bottled waters (Vandevijvere et al. 2009). Nutrient Reference Values are relevant to public policy in all these situations.

Fluoridated toothpaste and possibly other fluoride products are also crucial to caries prevention and are risk factors for dental fluorosis (Pendrys 2000; Do and Spencer 2007b). All such fluoride vehicles are ingested to some extent, more so in younger age children. All of them are capable of both preventing caries and leading to the occurrence of fluorosis. Nutrient Reference Values are also used to frame guidance on the use of such oral health products.

The studies by Dean from the 1930s and 1940s provide the best data for establishing the AI and UL due to the clear dose-response relationship observed between dental caries and fluorosis and concentration of fluoride in drinking water, derived by the same researchers at a similar time and on comparable populations. Furthermore, the fluoride intake is not complicated by other fluoride vehicles. The same cannot be said about the dose-response data systematically assembled in either substantial UK-based reviews in this century, the York and Cochrane reviews (McDonagh et al. 2000; Iheozor-Ejiofor et al. 2015). The dose-response data included in those reviews are limited to fluorosis and not caries, and they have been collected by different researchers in different countries at different times with the possibility of misspecification of the relationship due to general health (such as malnutrition) and specific oral health factors (the ingestion of fluoridated toothpaste).

It would be desirable for a contemporary data set to be available upon which to estimate an AI, optimum, and UL for fluoride intake. This would add confidence to the estimates from Dean's data. Such a "new" data set would need to

- include multiple population groups across the range of critical concentrations of fluoride in drinking water or that are associated with the prevention of dental caries and occurrence of fluorosis (negligible to at least 2.2 mg F/L or a little higher);
- estimate total fluoride intakes among children from drinking water, foods, beverages, and tooth brushing with a fluoridated toothpaste on a bodyweight basis (mg F/kg bw/d) for early child age groups;
- observe caries experience and the occurrence of fluorosis using standard indices in children some years later (or for children some years older at the same time if it is assumed there is no change in the pattern of fluoride intake over time);
- identify community preferences for the judgment about the balance between caries prevention and occurrence of fluorosis that can inform an AI, optimum, and UL of fluoride intake;
- establish an AI and UL on a bodyweight basis (mg F/kg bw/d) based on the available evidence;
- express these values as a total amount per day (mg/d), based on appropriate population data for the average bodyweight of infants and young children.

No such "new" data set seems readily available. Recent reports on Nutrient Reference Values for fluoride have not identified a suitable new data set. It might be argued that it would no longer be ethical or allowable to study a population group with drinking water with a fluoride concentration above 1.5 mg F/L. This is the upper limit allowed for in many drinking water standards (NHMRC 2011).

Hence, a practical path forward at present is to rework aspects of Dean's and McClure's research, which has been used in all subsequent reports such as the IOM and the EPA reports. The outcome would be Nutrient Reference Values that can bookend public policy on fluoride intake. Such reworking would resolve the conundrum of estimated fluoride intakes being higher than the old UL, yet adverse fluorosis not being observed. Such reworking might also add a further estimate, that of an optimum fluoride intake, to which current fluoride intakes in many countries might be more closely aligned.

Research on individual fluoride intakes in different contexts, including the relative source contribution of water, salt, or milk fluoridation, should continue. This would avoid the risk of leaving people with the impression that all dental fluorosis arises from fluoride in water supplies. The contribution of other fluoride sources, such as fluoridated toothpaste, needs to be regularly visited, especially with the trend toward higher fluoride concentration toothpastes.

Research since 2000 has suggested that a greater proportion of dental fluorosis risk is due to the use (and therefore swallowing) of fluoride-containing toothpastes than to optimally fluoridated water. A higher proportion of excess cases can be attributed to use of 1,000-ppm fluoridated toothpaste, swallowing slurry, and eating and licking of toothpaste than to drinking fluoridated water (Do and Spencer 2007b). This supports research that indicated that a greater proportion of cases of fluorosis (68%) can be attributed to fluoridated toothpaste in fluoridated area (Pendrys 2000). This level of information sheds light on why differences in caries prevention and occurrence of fluorosis are observed across time and populations.

More Nuanced Guidance on Fluoride Intake

Research on fluoride intake at an individual level is also needed to help inform policy to bring about change in fluoride intake or to alter the timing of fluoride intake across the critical period of ages 0 to 6 y for the occurrence of fluorosis. This extends from the issue of fluoride intake among infants being baby formula fed, to tooth brushing and toothpaste use, to the use of either home or professional fluoride products. Such research adds nuanced understanding on fluoride intake in specific contexts.

Some may consider it desirable to achieve considerable prevention of caries involving the use of fluorides without the occurrence of dental fluorosis at any severity. While this is a desirable aspiration, it seems out of reach at least for populations. Fejerskov et al. (1990) stated, "There exists no 'critical value' below which the effect of fluoride on dental enamel will not be manifest" (p. 697).

What should be aspired to is achieving near maximal caries prevention with the minimal occurrence of fluorosis and no fluorosis that would adversely affect ratings of oral health by the community. It might be possible that this aspiration can be achieved with a fluoride intake below that of the estimated AI. This would be all well and good. There may be population-level approaches to the use of fluorides in contexts where there is no water fluoridation program that reduces fluoride intake but still achieves caries prevention. An AI and UL are still useful bookends to evaluating fluoride intake, but the implications of such an assessment always need to be interpreted in the specific context of trying to improve oral health.

The Ultimate Outcome

The ultimate outcome of the consideration of fluoride intake, its relative source contribution, and timing in young children's lives is population-level monitoring of caries and dental fluorosis. Although the lag time between efforts to change the nature of fluoride intake and these outcomes is considerable, the lag is not unacceptable given that monitoring should be about finetuning fluoride intake for an optimal outcome. Desired alterations in fluoride intake need to be implementable, and change needs time to become widely adopted in a community.

There are examples of such finetuning successfully brought about decades ago with the lowering of the fluoride concentration in Hong Kong's water supply (Wong et al. 2014); to the efforts to reduce fluoride ingestion by preschool children in Australia though the availability of low fluoride children's toothpaste, and guidance on tooth brushing practices (Riordan 2002; Do and Spencer 2007c). Such monitoring should include assessment of community perceptions of caries and fluorosis and, if possible, some judgment of the relative benefit versus adverse effect of the use of fluorides to improve "oral health."

Conclusion

The dose-response relationship between fluoride concentration in water supplies and child caries and dental fluorosis underpins the estimation of an adequate and an upper limit benchmark for fluoride intake among children. Current benchmarks need revision. Estimation of an optimum fluoride intake requires consideration of the relationship of both caries and fluorosis to oral health. An optimum fluoride intake requires further consideration from an individual perspective and at a population level.

Notes

1. *City* in this context is synonymous with a *population group*.
2. Dean repeated the assessment of dental fluorosis in new cities included in the 21-city study of caries. In this review, only the original fluorosis data from the 22 cities data have been used when considering fluorosis. This excluded 8 cities included in the 21-city data. The basis for this exclusion is the lack of information on the distribution of Index of Dental Fluorosis scores (0.5, 1, 2, 3, 4) for the additional 8 cities. Precedent for this exclusion comes from the EPA (2010a).
3. Sometimes referred to as the Community Fluorosis Index.
4. It might be noted that this is a not dissimilar prevalence and distribution of fluorosis seen in fluoridated communities nowadays.
5. The occurrence of fluorosis at 0.0 mg F/L indicates that fluoride from foods can lead to fluorosis.
6. *Optimal* is used to describe the best or most favorable outcome associated with varying fluoride concentrations in a water supply, whereas *optimum* is a measure of the amount fluoride intake that produces the best or most favorable outcome.
7. Both the AI and UL are usually presented as mg F/kg bw/d and can be converted to mg F/d by multiplying by estimated average bodyweight for set age groups.

Author Contributions

A.J. Spencer, contributed to conception, design, and data acquisition, drafted the manuscript; L.G. Do, contributed to conception and data analysis, critically revised the manuscript; U. Mueller, J. Baines, contributed to conception, data analysis, and interpretation, critically revised the manuscript; M. Foley, M.A. Peres, contributed to conception and data interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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