



Australian Government
Department of Health



Australian and New Zealand Nutrient Reference Values for Fluoride

Supporting Document 3
Summary of previous reports

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Introduction

The following major publications alongside their related bibliography were reviewed in detail.

1. Institute of Medicine - Dietary Reference Intakes (DRI) for Ca, P, Mg, Vitamin D and Fluoride (IOM 1997)
2. York Review: A systematic review of water fluoridation (McDonagh et al. 2000)
3. European Food Safety Authority (EFSA 2005): Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Fluoride
4. National Research Council (NRC 2006) - Fluoride in drinking water: A scientific review of EPA's standards
5. US Environment Protection Agency (EPA 2010a and b) - Fluoride: Exposure and Relative Source Contribution (RSC) Analysis and Dose –response analysis for non-cancer effects
6. Scientific Committee on Health and Environment Risk (SCHER 2011) - Opinion on exposure to fluoride and the fluoridating agents of drinking water
7. EFSA 2013: Scientific opinion on dietary reference values (DRV) for fluoride – European Food Standard Authority

Details are given below of each of the eight publications, with an overview, review of methods, findings/estimates and the strengths, weaknesses and inconsistencies in each report.

Institute of Medicine Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride (IOM 1997)

Overview

Given the growing body of evidence on dietary intakes as well as better understanding of nutrient requirements and food constituents, the Food and Nutrition Board (FNB), Institute of Medicine (IOM), National Academy of Sciences, US considered that it was necessary to reassess the Dietary Reference Intakes (DRIs) for some of the nutrients, including fluoride, for the US population.

Method

The Adequate intake (AI) for fluoride was based on the fluoride content in drinking water that was associated with reduced dental caries without causing side effects which include moderate dental fluorosis. As fluoride is not an essential nutrient requirement, an estimated average requirement (EAR) could not be established. Based on published studies for water consumption in specific age groups and the fluoride content of food, the mean dietary fluoride intake in children and adults living in areas of the US with optimal fluoride levels during the 1930s was estimated to be 0.05 mg/kg bw/day. Dean (1942) showed that the reduction in dental caries was highest in children living in areas with fluoride content in drinking water close to 1 mg F/L (optimal fluoride concentration in drinking water) and that dental fluorosis was no more than mild (Dean's criteria) in these children. This in turn, prompted IOM to consider 0.05 mg/kg bw/day as the AI for fluoride both in children (excluding infants up to 6 months) and adults.

The Tolerable Upper Intake Level (UL) for fluoride is defined as the maximum level of total chronic daily intake judged unlikely to adversely affect the most sensitive individuals in a healthy population

A UL can be based on a no-observed-adverse-effect level (NOAEL – highest level of intake with no adverse effects) or a lowest-observed-adverse-effect level (LOAEL – lowest intake at which an adverse effect is detected) if the former is not available. Accordingly, a NOAEL of 1.9 mg F/L was selected as the endpoint for fluorosis. Establishing a UL usually involves considering an uncertainty factor (UF) to facilitate the extrapolation of study results to an entire population. A UF of 1 was chosen for the UL that is applicable for children up to 8 years old because the Dean study investigated the prevalence and severity of fluorosis in a large cohort (n=5824) of 12–14 year old children exposed to differing concentrations of fluoridated drinking water. Since the severity of fluorosis is related to the duration, timing, and dose of fluoride intake, cumulative exposure during the entire tooth maturation stage was considered in this study and therefore the uncertainty in the water fluoride concentration-fluorosis severity relationship was considered to be low.

Findings/estimates

For infants aged 6 months and below the AI was estimated to be 0.01 mg F/day (0.001–0.003 mg F/kg bw/day) based on the fluoride content in human milk. For all other ages the

AI was 0.05 mg F/kg bw/day. Using the average body weight the recommended AI was expressed as a per day intake for all age groups (7–12 months, 1–3 years, 4–8 years, 9–13 years and 14–18 years) except for adults aged 19+ years where the average body weight was calculated for each sex.

The IOM stated that at the optimal fluoride concentration of 1 mg F/L in drinking water the estimated dietary fluoride exposure in children aged between 1 and 9 years ranges between 0.02 and 0.10 mg F/kg bw/day (see Table 3.5, main report). In the derivation of a UL for children, IOM selected a fluoride concentration of 2 mg F/L in drinking water from the Dean (1942) data because it considered that there is likely to be less than a 5% prevalence of moderate dental fluorosis in children. However, at this fluoride concentration in drinking water the IOM also estimated that dietary fluoride intakes would only range between 0.08 and 0.12 mg F/kg bw/day. The body weights and more importantly the water intakes used in this dietary fluoride intake estimate were not provided. It is nevertheless remarkable that the upper range of fluoride intake estimate of 0.12 mg F/kg bw/day at 2 mg F/L drinking water is only slightly higher than the corresponding upper range estimate of 0.10 mg F/kg bw/day with a fluoride concentration of 1 mg F/L in drinking water.

The IOM established a UL of 0.10 mg F/kg bw/day by averaging the chronic daily fluoride intake range of 0.08–0.12 mg F/kg bw/day for infants, toddlers, and children through to 8 years of age. For children older than 8 years and adults the UL was estimated to be 10 mg F/day based on a NOAEL of 10 mg F/day for the development of skeletal fluorosis. This UL of 10 mg F/day was also considered appropriate for pregnant and lactating women.

Strengths/weaknesses/inconsistencies

The report provides a comprehensive assessment and derivation of reference values for calcium and related nutrients including fluoride, though confined to the US. IOM have reassessed the DRI for calcium and related nutrients including fluoride. The derivation of the UL of 0.10 mg F/kg bw/day for fluoride is consistent with drinking water at the optimal fluoride concentration for dental caries but appears to be inconsistent with the reported NOAEL of 1.9 mg F/L for less than a 5% prevalence of moderate dental fluorosis. One of the strengths of the Dean study was that it was undertaken in an era where fluoride intake was confined to fluoride in water. A wide range of studies were reviewed although a specific search/assessment strategy was not specified.

York Review (McDonagh et al. 2000): A systematic review of water fluoridation

Overview

Increasing evidence that water fluoridation prevents dental caries and thereby reduces inequality in dental health prompted the Department of Health, UK to assign the York Review team to conduct a comprehensive systematic review on the efficacy and safety of water fluoridation. The main purpose of the review was to detect the evidence on the positive and negative effects of water fluoridation in preventing dental caries. Nonetheless, McDonagh and colleagues did not attempt to address the issues of either an AI or UL for fluoride.

Method

A preliminary search was conducted on Medline and Embase databases to identify the availability of reviews and the size of evidence on the effects of water fluoridation. Based on the preliminary search, 25 specialist databases including Medline and Embase were searched from the inception of the database to June/October 1999. Relevant journals as well as Index Medicus (1945–63) and Excerpta Medica (1955–73) were hand searched. Bibliographies of all included studies and the World Wide Web were also searched. The public was informed about the purpose, method and progress of the review via a web page which was designed and maintained by the NHS Centre for Reviews and Dissemination (NHSCRD), University of York. Updating the search was carried out using Medline, Embase, Toxline and the Current Contents (Science Citation Index) while Endnote was used to identify and remove duplicate records.

Based on the issue of handling the risk of bias (selection, confounding and measurement) studies were graded into three levels of evidence ranging from highest to lowest quality – level A, B and C. For assessment of positive effects, studies with evidence below level B were not considered while all levels of evidence were considered for evaluating negative effects. Papers for inclusion were assessed by three independent reviewers based on some pre-determined criteria including primary, human only studies directly related to fluoride in drinking water where two groups with different fluoride levels in water were compared. Articles in languages other than English were also assessed for inclusion and extracted using translators.

Two independent reviewers assessed study validity that was based on a modified checklist from NHSCRD. A validity score was assigned for each study included according to the number of checks achieved. DMFT/dmft and the proportion of caries free children were the two outcomes measured in studies assessing the effect of water fluoridation on caries experience. The effect measure was the difference in caries prevalence between baseline and the final examination in the fluoridated area compared to the children of the same age in the control area. In regards to negative effects, since dental fluorosis had been measured using various indices in different studies, it was defined as any score other than normal on each index.

Measures of effect with their 95% confidence intervals (CI) were plotted on forest plots. Visual examination of plots and statistical tests (Q statistic) were used to check for heterogeneity. When there was no evidence of statistically significant heterogeneity a meta-analysis was conducted and a pooled estimate effect measure was provided. If heterogeneity was statistically significant, meta-regression was performed to explore and explain sources of heterogeneity. Multi-level regression analysis was used to combine studies and to determine the association between fluoride content in water and dental fluorosis while a multi-level model was used to combine studies.

Findings/estimates

None of the studies that met inclusion criteria (n=254) yielded level A evidence. Studies with level B evidence suggested that water fluoridation reduces caries prevalence, as measured by the proportion of caries-free children and by the mean dmft/DMFT score although the available evidence did not show clearly the amount of caries reduced. The mean difference in the percentage of caries-free children ranged from -5.0% to 64%, with a median of 14.6% while mean change in dmft/DMFT score was from 0.5 to 4.4 with a median of 2.25 teeth. The number needed to treat (NNT) for all teeth combined was estimated to be 6 (median): 6 people need to receive fluoridated water for one extra person to be caries-free (95% CI: 5–9). Apparently caries prevalence increased when water fluoridation was discontinued as suggested by level B evidence.

Out of 88 studies included to analyse dental fluorosis all but one provided level C evidence. Nonetheless they point to a dose-response relationship between water fluoride level and fluorosis prevalence with a pooled estimate of 48% (95% CI: 40%–57%) at a water fluoride concentration of 1 mg F/kg. However, the estimate for fluorosis of aesthetic concern was lower (12.5%, 95% CI 7.0 to 21.5). Out of 29 studies on the association between water fluoridation and bone fractures (mean validity score =3.4), 28 were of evidence level C. There was a significant heterogeneity among studies and no clear association between fluoridation and bone fractures. There were 26 studies – 21 of which were of evidence level C - included to assess the association between water fluoridation and cancers. None of them provided conclusive evidence for any association. Likewise, there was no evidence to support other adverse effects pertinent to water fluoridation. The authors concluded that although the quality of evidence was low there was an overall reduction in caries, which can be attributed to water fluoridation, and that such evidence should be considered along with the increased prevalence of fluorosis.

Strengths/weaknesses/inconsistencies

One of the main strengths was the extensive nature of the review which was based on 25 databases and had been extended from late 1930s to 2000; an independent review process, completeness of retrieval, transparency to the public and the search strategy that was extended to non-English articles were among other positive points. Studies were restricted to 'before' and 'after' studies, excluding cross-sectional studies.

The authors admitted that the overall quality of the research reviewed was of low to moderate quality. Publication bias usually tends to publish positive (statistically significant) findings and this review - though comprehensive - was no exception to that and consequently might have over-estimated the effect under study. The scoring system used for

validity assessment of studies was not sensitive enough to detect how well they were carried out although items on the list were ticked.

European Food Safety Authority (EFSA 2005); Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Fluoride

Overview

EFSA was asked to review the upper levels of daily intakes in some nutrients including fluoride in regard to adverse health effects and in view of establishing safety factors where necessary.

Method

A wide range of studies was reviewed though a specific strategy was not available.

Findings/estimates

The UL for fluoride for children aged 1–8 years was considered to be 0.1 mg F/kg bw/day based on less than 5% prevalence of moderate fluorosis, which was in line with IOM, 1997. The Panel did not consider an uncertainty factor for this age group as the UL was derived from population based studies. For children aged over 8 years and adults, an uncertainty factor of 5 was applied to derive a UL of 0.12 mg F/kg bw/day which is equivalent to a UL of 5 mg F/day in children aged 9–14 years and 7 mg F/day for age 15 years and older, including pregnant and lactating women. An uncertainty factor of 5 was applied because the study which investigated skeletal fluorosis in elderly postmenopausal women was of relatively short duration and it was not designed to define a LOAEL.

This was based on fluoride intake from all sources including water and dental healthcare products and considering bone fracture as the critical endpoint. The EFSA Panel noted that fluoride intake from food and water in 1–8 year old children was well below the UL if the fluoride content of their drinking water was not higher than 1.0 mg F/L. The inappropriate use of dental care products, in particular fluoridated toothpaste, has been the main reason behind increased prevalence of mild dental fluorosis in some countries according to the Panel. Given that fluoride intake in breast-fed infants is very low, infants are not at risk of developing enamel fluorosis and thus a UL for infants was not established. It was estimated that using water with fluoride content over 0.7 mg F/L for preparation of powdered formula would eventually cause an exceedance of the maximum recommended fluoride level of 0.6–0.7 mg F/L in infant formula.

The EFSA Panel was of the view that the chance of exceeding the UL of 5/7 mg F/day on a normal diet would be relatively low in children aged more than eight years and in adults.

Strengths/weaknesses/inconsistencies

An array of sources was reviewed; however, no search strategy is available in the report. An AI was not been considered in the estimations.

US National Research Council (NRC 2006) - Fluoride in drinking water: A scientific review of EPA's standards

Overview

Exposure standards for contaminants in public drinking water are based on the maximum contaminant level goal (MCLG), the maximum contaminant level (MCL) and the secondary maximum contaminant level (SMCL). MCLG is the level at which no adverse health effects are expected to occur, MCL is the enforceable standard set as close as possible to the MCLG taking into account other factors including cost and treatment technology and SMCL is the level where no cosmetic or aesthetic effects occur. For fluoride level in drinking water, the Environment Protection Authority (EPA) established 4 mg F/L as the standard for MCLG and MCL, respectively, and 2 mg F/L for SMCL in 1986 and the NRC reviewed and concluded them as appropriate in 1993 despite recommending further research. Given the availability of new research on fluoride and the need for periodic assessment of regulations for drinking water contaminants, EPA requested NRC to re-evaluate the adequacy of MCLG and SMCL for fluoride. However, evidence on a dental caries prevention effect of fluoride in drinking water or a risk-benefit assessment of artificial water fluoridation or issues relevant to establishing an AI/UL was not considered in this review.

Method

A specific search strategy was not described. Material including research articles, position papers and unpublished data available after the 1993 NRC report was reviewed. A general weight-of-evidence approach, assessing multiple lines of evidence from in vitro assays, animal research and human studies to suggest a human health risk, was used.

Findings/estimates

Toxicity end points considered for assessing the adequacy of MCLG and SMCL were severe enamel fluorosis, skeletal fluorosis and bone fractures. The committee was of the view that the overall prevalence of severe enamel fluorosis was about 10% among children in the US where water fluoride concentrations were at or near the MCLG of 4 mg F/L and hence the MCLG was not adequate to protect children from this condition. Cosmetic concern of moderate enamel fluorosis was, however, not detected given the inability of the current indices to differentiate between enamel fluorosis of anterior and posterior teeth as well as varying distribution patterns of enamel fluorosis among teeth.

Based on the available evidence the committee concluded that the MCLG of 4 mg F/L should be lowered to stop children from developing severe enamel fluorosis and to cut the lifetime accumulation of fluoride into bone, particularly in subpopulations that were at risk, and thereby reduce the incidence of bone fractures and skeletal fluorosis even though more evidence was required to confirm the interrelationship between fluoride ingestion, bone fractures and skeletal fluorosis. To lower the MCLG, the committee suggested that the fluoride risk assessment should be updated by including new health risk information and total exposure be better estimated as relative source contribution for individuals. Despite

the prevalence of severe enamel fluorosis being almost zero at fluoride concentrations below 2 mg F/L (SMCL), they were of the view that the occurrence of moderate enamel fluorosis cannot be totally eliminated at the level of SMCL. However the prevalence of cosmetically significant moderate fluorosis at this concentration was estimated to be less than 15% which was in line with the expectation of EPA.

Strengths/weaknesses/inconsistencies

Not applying/not adequately describing a search strategy was the major limitation of the review and thus the readers cannot get an insight into either the search criteria or the assessment process of the material being reviewed.

US EPA (EPA 2010a) - Fluoride: Exposure and Relative Source Contribution Analysis

Overview

Following the recommendation of NRC 2006 report to lower the MCLG of 4 mg F/L in drinking water, the US EPA Office of Water was assigned the task of quantifying exposure and relative source contribution analysis of fluoride.

Method

Peer-reviewed and published data from the US and Canada for public and consumer water systems were used in the evaluation. Dietary exposures were derived from published studies and no independent evaluation was carried out by EPA.

Findings

Drinking water was the highest single contributor to total fluoride intake in all age groups ranging from 40% in 1–10 year olds, 60% in those aged above 14 years to 70% in infants aged 6–11 months. A higher contribution from drinking water in infants could be attributed to using powdered formula reconstituted with tap water containing fluoride. Interestingly, children who were at a higher risk of developing dental fluorosis had a relatively low fluoride intake from drinking water (40%) compared to adults (60%). Food and beverages in combination accounted for about 45% of total fluoride intake in 4–11 year old children while toothpaste was another significant contributor (20–25%) in children aged between 1–4 years. The authors indicated that fluoride exposure level in some young children up to about age 7 might increase the risk for severe dental fluorosis, while contribution from residential tap water to the total fluoride intake was lower than that it had been in the past. In the commercial beverage industry, use of fluoridated water may have contributed to increased dietary fluoride from beverages, resulting in over-exposures. Timing, frequency and duration of the over-exposures affect the impact of the increased fluoride intake on developing severe dental fluorosis. The risk for severe dental fluorosis was greater for children living in areas where fluoride content in water is close to the MCL (4 mg F/L).

Strengths/weaknesses/inconsistencies

One of the main strengths was the comprehensive nature of the review where exposure and RSC of fluoride were analysed. Some of the drawbacks were using published data from the US and Canada only and not describing a specific method of selection or assessment of studies for the review.

US EPA (EPA 2010b) - Fluoride: Dose-Response Analysis for Non-Cancer Effects

Overview

Subsequent to the publication of NRC 2006 report on fluoride in drinking water, the US EPA started reassessing dose-response effects of fluoride on severe fluorosis and bone (EPA 2010b).

Method

Given that the recent studies investigating the association between fluoride in drinking water and its adverse effects, including dental fluorosis, have been confounded by several factors, such as worldwide popularity of fluoridated toothpastes and mouth rinses and presence of fluoride in processed food and beverages, it was hard to quantify total fluoride intake in dose-response analyses. Thus the US EPA decided to include historical studies conducted before the availability of such fluoride products and accordingly the Dean (1942) study, which is considered as one of the earliest studies with a sufficiently large sample size and a standard protocol to document the prevalence and severity of dental fluorosis, was selected. A categorical analysis (CATMOD) and a Benchmark Dose (BMD) analysis were performed using the Dean (1942) data.

Estimates/findings

Categorical analysis pointed to a positive correlation between fluoride content in water and Dean's fluorosis index and indicated that severe fluorosis levels could be predicted by high fluoride content in water. Using a 0.5% prevalence of severe dental fluorosis in children as an acceptable endpoint, several mathematical models were tested for goodness-of-fit to the Dean's data. The best fit as judged by the smallest Akaike Information Criterion value was observed with the dichotomous Hill model. Using this model the Benchmark Dose (BMD) was calculated to be 2.14 mg F/L and the BMDL (lower 95% bound for BMD) was 1.87 mg F/L. As expected the BMD and BMDL corresponded well to the LOAEL of 2.2 mg F/L for a 0.7% prevalence of severe fluorosis and a NOAEL of 1.9 mg F/L, respectively.

In the absence of drinking water intake data in Dean's study, indirect estimation of age and drinking water consumption-specific fluoride dose was performed. Tap water consumption estimates for children were based on the 1977/1978 Nationwide Food Consumption survey (NFCS) conducted in the United States (Ershow and Cantor 1989). It was reported that these data were used in the dose analysis because they were collected during a time period closer to the Dean study. At mean tap water consumption (with a fluoride content of 1.87 mg F/L), the estimated fluoride intake for children aged 1 to 14 years ranged from 0.04 mg to 0.09 mg F/kg bw/day. However, at the 95th percentile of tap water consumption the estimates ranged from 0.08 to 0.19 mg F/kg bw/day. In selecting the oral reference dose (RfD) only the levels greater than 0.05 mg/kg bw/day were considered and 0.07 mg/kg bw/day was nominated. The US EPA considered this level to be suitable to account for the contribution from drinking water given that it provided a realistic difference in exposure between it and the AI (0.05 mg/kg bw/day) recommended by the IOM (1997). However, since this derived

RfD did not include any fluoride from food an additional 0.01 mg/kg bw/day was added to give a total oral RfD of 0.08 mg F/kg bw/day.

The EPA could not find any study for evaluating dose-response skeletal effects of fluoride. The total oral RfD recommended by US EPA, which is equivalent to a dose of 5.6 mg F/day for a 70 kg adult, is well below the NRC (8 mg F/day) and WHO (14+ mg F/day) benchmarks for risk of fluoride-induced bone fracture in adults.

Strengths/weaknesses/inconsistencies

Analysis of the Dean (1942) data was critical as well as comprehensive and calculation of various exposure levels for each age group was based on a BMDL (lower 95% bound for BMD) of 1.87 mg F/L. The RfD was determined by considering the central tendency estimate (i.e. the 50th percentile (median) or mean of the log-normal distribution) of fluoride intakes with drinking water fluoridated at 1.9 mg F/L for each age group. This estimate was then adjusted upwards to be greater than the AI value of 0.05 mg F/kg bw/day by arbitrarily selecting 0.07 mg F/kg bw/day as the RfD. A further 0.01 mg/kg bw/day was also added for the likely contribution of fluoride from food to arrive at the final RfD value of 0.08 mg F/kg bw/day. In addition, limitations in the Dean (1942) study including non-availability of information on drinking water intake and restricting the sample only to white children might have affected the outcome of the analysis and extrapolation of the findings to current populations.

EC Scientific Committee on Health and Environment Risk (ECSCHER 2010): Opinion on critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water

Overview

The European Commission assigned the Scientific Committee on Health and Environmental Risk (SCHER) the task of providing scientific advice on public health and the environment on a regular basis. As part of this task and in the context of continuing debate over the practice of intentional water fluoridation amidst pressure from anti-fluoride groups, SCHER was requested to provide its scientific opinion by critically reviewing new evidence on fluoride in 2010.

Method

Although information on a specific search strategy was lacking, SCHER reviewed journal articles including reviews and reports as well as all papers. The public was informed to provide relevant information online and the preliminary opinion was available for 3 months for public consultation. Assessment of the information was done by a weight-of-evidence approach developed by the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). A health risk assessment of fluoride within epidemiologic studies, both human and animal experimental studies as well as cell culture studies was performed and the evidence was weighed together to make a combined assessment. In particular, evidence was obtained that became available after publication of the Scientific Committee on Consumer Products (SCCP) opinion on fluoride in dental care products and the EFSA opinion on a tolerable UL of fluoride in 2005. However material available before 2005, which was not considered by SCCP and EFSA panels was also reviewed.

Findings/estimates

Based on available evidence SCHER concluded that early enamel fluorosis in EU children is associated with daily intake of fluoride in both fluoridated and non-fluoridated areas for which a threshold cannot be determined. While skeletal fluorosis has not been an endemic problem in the EU there was not sufficient evidence to support a link between fluoride and bone fractures at the current water fluoride concentration in fluoridated areas. Neither animal studies nor epidemiological studies provide evidence for carcinogenicity, neurotoxicity, reproductive and developmental effects of fluoride at concentrations permissible in drinking water.

The main source of fluoride exposure in the general population was fluoride in drinking water. Use of fluoridated toothpaste (0.05 -0.15% fluoride in toothpaste) in 2–6 year old children could contribute to almost one quarter of total systemic dose ranging from 10% ingested (0.05% F in toothpaste, supervised) to 40% ingested (0.15% F in toothpaste, unsupervised), depending on the concentration of fluoride in toothpaste and the amount

ingested. Data were of not of sufficiently high quality to undertake a full uncertainty analysis. The panel was of the view that both topical and water fluoridation prevent dental caries, mainly on permanent teeth.

There was no new evidence to change the established values for the UL by EFSA in 2005: children 1–3 years - 1.5 mg/day; children 4–8 years – 2.5 mg/day; 9–14 years – 5 mg/day; 15 years or more - 7 mg/day. No UL for infants aged below one year was established but the fluoride intake in breast-fed infants was much lower than that in formula-fed infants.

Fluoride intake in adults and children aged above 12 years was below the UL in most areas except where fluoride level in water exceeded 3 mg F/L and with high water consumption. For 6–12 year and 1–6 year old children, the UL was not exceeded if they lived in areas with water fluoride content less than 1.5 mg F/L and consuming water less than 1 L and 0.5 L/day, respectively, and used fluoridated toothpaste within the recommended quantity. Based on available evidence the panel concluded that adding fluoride to water at levels between 0.8–1.5 mg F/L posed no undue risk.

While highlighting the importance of developing new biomarkers for long-term exposure as well as standardized methods for exposure assessment the panel considered that risk assessment is essential for studying health effects. It was also emphasised that cohort studies be used to establish fluoride content in food and its bioavailability as well as to explore the role of fluoride in dental fluorosis and caries prevention. The panel expected that these activities would fill the information gap pertinent to exposure assessment and health effects of fluoride.

Strengths/weaknesses/inconsistencies

One limitation is non-availability of a specific search strategy. However, making a combined assessment of the information by means of a weight-of-evidence approach and consulting public opinion in obtaining the relevant information, are some strong points of the report.

European Food Safety Authority (EFSA 2013): Scientific Opinion on Dietary Reference Values for Fluoride

Overview

In light of emerging evidence and as part of reviewing the existing population reference intakes for energy, micro- and macro-nutrients, EFSA was requested by the European Commission to provide a scientific opinion on DRV for fluoride.

Method

An array of sources were reviewed. However, the authors did not mention a search or assessment strategy for material under review.

Findings

The EFSA panel was of the view that there was no consistent evidence to use biomarkers for fluoride to establish intake of fluoride or to set a DRV for fluoride. Considering the beneficial effects of fluoride in caries prevention EFSA believed that establishing an AI was more appropriate. Studies conducted before 1970s have shown an inverse relationship between caries experience and fluoride concentration in water – the main strength of these studies was that drinking water was virtually the only source of fluoride intake at that time. These studies suggested that the optimal concentration of fluoride in water where maximum caries protection effect was achieved was 1 mg F/L while the prevalence of mild fluorosis was 10% at this level. The average daily fluoride intake of a child from diet and drinking water at this optimal level was estimated to be 0.05 mg F/kg bw/day and this was in line with the IOM (1997) findings. The studies conducted after 1970s were biased by the fluoride intake from other sources including dental products and majority of them did not provide information on total fluoride intake which in turn had limited use in making conclusions about dose-response relationships between fluoride intake and caries experience. Neither was there sufficient data for the dose-relationship between fluoride and caries for adults nor total intake of fluoride for European populations. The available data suggest that total intake may vary at or below 0.05 mg F/kg bw/day.

Based on the available evidence the EFSA panel recommended that the AI for fluoride from all sources should be 0.05 mg F/kg bw/day for both children and adults including pregnant and lactating women. This is based on estimates of fluoride intakes from diet and drinking water with a fluoride concentration where maximum caries preventive effect and minimum fluorosis risk are achieved.

Strengths/weaknesses/inconsistencies

On the plus side, a broad range of material has been reviewed. However, the review was of a more narrative nature with no specific search strategy or assessment process being described. No estimates for a UL were made.

References

Dean HT 1942. The investigation of physiological effects by the epidemiology method, in: Fluoride and Dental Health, Publ. Amer. Assoc Advanc. Sci.; 19: 23–31.

Environmental Protection Agency (EPA) 2010a. Fluoride: Exposure and Relative Source Contribution Analysis, Office of Water, Washington, DC. EPA 820–R–10–015. <http://water.epa.gov/action/advisories/drinking/upload/Fluoridereport.pdf>. Accessed – 3 April 2014.

Environmental Protection Agency (EPA) 2010b. Fluoride: Dose-Response Analysis For Non-cancer Effects Office of Water, Health and Ecological Criteria Division, Washington, DC.USA, EPA 820–R–10–019. http://water.epa.gov/action/advisories/drinking/upload/Fluoride_dose_response.pdf. Accessed – 3 April 2014.

Ershow AG, Cantor KP 1989. Total water and tapwater intake in the United States: population-based estimates of quantities and sources, National Cancer Institute Contract No. 263–MD–810264, Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD.

European Food Safety Authority (EFSA) 2005. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Fluoride, EFSA Journal; 192: 1–65. doi:10.2903/j.efsa.2005.2192.

European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies (EFSA NDA) 2013. Scientific opinion on Dietary Reference Values for fluoride, EFSA Journal; 11(8): 3332–78. doi:10.2903/j.efsa.2013.3332.

Institute of Medicine (IOM) 1997. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride, Food and Nutrition Board, IOM, National Academy Press, Washington, DC, USA, pp 288–313.

McDonagh M, Whiting P, Bradley M, Cooper J, Sutton A, Chestnutt I, et al. 2000. A systematic review of water fluoridation (York Review), NHS Centre for Reviews and Dissemination, University of York. York: York Publishing Services Ltd. 125pp. https://www.york.ac.uk/inst/crd/CRD_Reports/crdreport18.pdf. Accessed – 3 April 2014.

National Research Council (NRC) 2006. Fluoride in drinking water. A scientific review of EPA's standards, Committee on Fluoride in Drinking Water, National Research Council, National Academies Press. 530pp. http://www.nap.edu/openbook.php?record_id=11571&page=1. Accessed – 3 April 2014.

Scientific Committee on Health and Environmental Risk (SCHER) 2011. Opinion on critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water, European Commission, 16 May 2011. 59pp. http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_122.pdf. Accessed – 3 April 2014.