



820-R-10-014

COMMENT-RESPONSE SUMMARY REPORT
for the
PEER REVIEW
of the
Fluoride:
Exposure and Relative Source Contribution Analysis
DOCUMENT

November 2010

Office of Water
Office of Science and Technology
Health and Ecological Criteria Division

U.S. Environmental Protection Agency
Washington, D.C. 20004

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ACKNOWLEDGMENTS

This document was prepared with the technical assistance of the Toxicology and Hazard Assessment Group of the Environmental Sciences Division of Oak Ridge National Laboratory, Oak Ridge, Tennessee, under EPA IA No. DW-89-92209701 and DOE IAG No. 1824-S881-A1. Principal EPA Scientists are Joyce Morrissey Donohue, PhD, and Tina Duke, MPH, Health and Ecological Criteria Division, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency, Washington, DC.

The Oak Ridge National Laboratory is managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

I. INTRODUCTION

The United States Environmental Protection Agency (EPA), Office of Water is charged with protecting public health and the environment from adverse exposure to chemicals and microbials in water media, such as ambient and drinking waters, waste water/sewage sludge and sediments. In support of this mission, the Office of Water/Office of Science and Technology (OST) develops health standards, health criteria, health advisories, and technical guidance documents for water and water-related media. Under this work assignment, documents prepared by OST are to undergo external peer review.

Peer review is an important component of the scientific process. It provides a focused, objective evaluation of a research proposal, publication, risk assessment, health advisory, guidance or other document submitted for review. The criticisms, suggestions and new ideas provided by the peer reviewers ensure objectivity, stimulate creative thought, strengthen the reviewed document and confer scientific credibility on the product. Comprehensive, objective peer review leads to good science and product acceptance within the scientific community.

The Peer Review for “*Fluoride: Exposure and Relative Source Contribution Analysis*” was conducted on May 14, 2010, in Washington, DC, to allow the external peer reviewers to discuss their evaluations of the EPA/OW document. The Peer Review was conducted under EPA Contract Number EP-C-07-059 (Work Assignment 2-02) to Eastern Research Group, Inc., 110 Hartwell Avenue, Lexington, MA.

The list of external peer reviewers and their affiliations are shown below:

Linda C. Abbott, Ph.D., Regulatory Risk Analyst, Office of Risk Assessment and Cost-Benefit Analysis, U.S. Department of Agriculture

Mary A. Fox, Ph.D., Assistant Professor, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health.

E. Angeles Martínez Mier, DDS, MSD, Ph.D., Associate Professor, Department of Preventive and Community Dentistry, Indiana University School of Dentistry

David L. Ozsvath, Ph.D., Professor of Geology and Water Science, Department of Geography/Geology, University of Wisconsin-Stevens Point

II. CHARGE TO THE PEER REVIEWERS

1. Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.
2. Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.
3. Please consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may have for alternative studies that you believe are more representative of exposures.
4. Please comment on EPA’s rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically justified and clearly and objectively described? What changes or improvements would you suggest?
5. Please comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication, as supported by the concentrations found in various food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940’s?
6. Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.
7. Please provide any additional comments and/or further suggestions you may have for improving the document.

III. PEER REVIEW COMMENTS AND EPA RESPONSES

Charge Question 1. Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.

Reviewers noted agreement in their written comments that the purpose of the draft RSC Analysis was not clearly stated and that adding an overview or “road map,” including a statement of objectives, in the introductory section of the document would help address this concern.

EPA Response: Dr. Donohue noted that the Agency agreed with these pre-meeting comments, and had decided to add forwards to both the RSC Analysis and the Dose-Response Report in order to outline the study objectives and present a road map. She said that EPA planned to post both documents on the Internet at the same time. Dr. Donohue also noted that the external peer reviewers, as well as EPA internal reviewers, had clearly indicated confusion around presentation of how the Agency used the McClure (1943)¹ data to estimate food contributions in 1942. She proposed that EPA would remove the description of the McClure (1943) data from the draft RSC Analysis and add it as an appendix to the Dose-Response Report. This seemed appropriate since those data are used in the Dose-Response Report rather than the RSC Analysis. She asked reviewers for feedback on whether they thought this change would address their concern about this section of the report.

Reviewers supported the idea of a forward and agreed to talk about the best location for the McClure (1943) data when they discussed Charge Question 5.

Dr. Ozsvath remarked that it was difficult to determine what the critical steps of the analysis were and why they were taken. He had alluded to this concern in his written response to Question 1 and elaborated on it in his response to Question 7 (see Appendix F). He noted that this concern was also echoed in Dr. Abbott’s detailed written comments. He recommended that the document include a road map, a list of objectives, and a statement at the end of the document clarifying how the objectives were met.

EPA Response: EPA has prepared a preface to the exposure and RSC document which states the objectives of the effort and the over arching factors that governed the EPA analytical approach. The requested map of the assessment is included in the preface.

The last chapter provides a statement on how the objectives of the document have been met.

Dr. Martinez Mier noted that some of the terminology was not consistently used throughout the document. Also, some of the steps in the fluoride analysis are not consistent with those found in the current dental literature for fluoride analysis. Though the document is not intended for the

¹ McClure, F.J. 1943. Ingestion of fluoride and dental caries. Quantitative relations based on food and water requirements of children 1-12 years old. Amer. J. Dis. Child. 66:362. [Republished in Publication 825, U.S. Public Health Service, 1962].

dental community, it will inevitably be circulated within that community because it impacts dental fluorosis and caries prevention. Dr. Martinez Mier referred EPA to her written response to Charge Question 1 (see Appendix F) for specific suggestions about reorganizing the discussion of analytical methods and changing how things are referenced in order to bring the discussion more in line with contemporary analytical approaches used by the dental community.

EPA Response: The information on analytical methods was prepared by an analytical chemist. It was included to provide background on the methods that were used by the researchers who conducted the published studies included in the report. This limitation is now included in the preface to the report. EPA acknowledges that there have been improvements in the methods used to measure fluoride in different media, however the methods used more recently are, for the most part, not those that were used for the analyses cited in this report.

Dr. Fox said she agreed with recommendations to improve clarity and transparency by stating the questions the document will address and the approach EPA used to address those questions. She also had concerns about the discussion of public health implications in Chapter 8. She had provided a detailed comment about this in her written response to Charge Question 7 and noted that she would talk about this in detail when Question 7 was discussed.

EPA Response: The Preface mentioned in the response to the first comment lays out the objectives for the exposure and RSC document and the factors governing the approach that EPA used in its development. The absence of discussion of public health implications in Chapter 8 was a deliberate omission because the public health implications extend beyond the purview of the EPA and impact fluoridation guidelines (Centers for Disease Control) as well as the role of the Food and Drug Administration with its oversight of toothpaste, bottled water, and food labeling. EPA has since entered into discussions with Health and Human Services about the findings of the exposure and RSC analysis. The outgrowth of those discussions may promote inclusion of more information on public health implications of the EPA findings. EPA did expand the original closing paragraphs of Chapter 8 to provide statements on the major findings of the document relative to risk.

Dr. Abbott referenced all of her written comments in response to Charge Question 1 (see pages F-6 to F-8 of Appendix F). She also noted one additional comment. She recommended that, at the beginning of the document, EPA acknowledge the spectrum of populations obtaining drinking water from the full variety of sources, including community water supplies, spring water, bottled water, and well water, and clarify whether these sources factor into the MCL. The document seems to combine these at different levels in the RSC calculation because food intake is considered across the population as a whole, not just in those who drink community water. This is a particular problem when considering beverages. For example, beverages prepared by adding water and made away from home, like tea or beverages made from dry powders with extra indirect water, may not come from the same water supply used at home. In the Continuing Survey of Food Intakes by Individuals (CSFII), all these different types of water sources are associated with the different types of food and beverages. The document should acknowledge from the outset that the analysis combines these different populations for different parts of the estimate. Without this acknowledgment, readers will be confused when they learn that the document only considers populations served by community water systems and not those who are

not served by those systems but who are exposed to fluoride in their diet by ingesting food or beverages made with fluoridated water (e.g., at a processing plant).

EPA Response: In response to this comment, Dr. Donohue clarified that EPA used data from the Food and Drug Administration’s (FDA’s) total diet study, which clearly identified in the market basket which beverages were made from public water and which at home. In the analysis, EPA subtracted out the portion of beverages made with public water.

Dr. Abbott responded that the CSFII would provide a more refined estimate of the source of indirect water used in beverage preparation.

EPA Response: Dr. Donohue clarified that EPA relied on the published literature for the RSC Analysis and did not conduct any independent analyses.

In light of that clarification, a reviewer suggested that EPA state at the beginning of the document that the Agency had not conducted any new analyses and instead had relied exclusively on the literature. Other reviewers agreed it was important for EPA to more clearly explain what they did and did not do in the analysis.

EPA Response: As mentioned earlier, EPA added a preface to the document which explicitly states the bounding conditions for the EPA analysis. The Introduction lays out the Agency policies that govern the RSC analysis. Some revisions have been made to that section in order to increase its transparency.

EPA’s age-specific drinking water intake data consider both direct and indirect drinking water intake as reported in the most recent Continuing Survey of Food Intake by Individuals (1994-1998). When EPA selected the studies that represented the exposures for each age group of concern, studies where home-prepared beverages were reconstituted with deionized-distilled water were used if they were available, and plain tap water intake was not included in the beverage category. If the only available data came from market basket studies that did not require home-prepared beverages to be reconstituted with deionized-distilled water, the locality with the lowest level of fluoride was selected to represent the age group and the fluoride concentration of the local drinking water was provided in the data summary Table. The studies selected did not include plain drinking water in the beverage category.

EPA obtained information on the home-prepared beverages in the present and prior FDA market baskets and presents that information in the report, thereby providing perspective on the uncertainties that might result from the use of market baskets that could have used tap water for beverage preparation. The uncertainties in the beverage data from the key studies are discussed in the text.

Charge Question 2. Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.

Reviewers agreed that the document should provide a better discussion of uncertainty. Individual comments included:

- The draft RSC Analysis describes sources of uncertainty, but does not attempt to show how the RSC would be affected if different assumptions were made. A sensitivity analysis would help show how different assumptions would affect the RSC. Page 113 of the draft document states that the Agency believes these are reasonable estimates, but the Agency does not justify this statement; this part needs more scientific rigor.
- The draft RSC Analysis recognizes some sources of uncertainty (e.g., “technological limitations”), but should be more explicit in discussing the uncertainties associated with specific values from various studies related to fluoride analysis. The fact that uncertainty in fluoride analysis can go either way (leading to much lower or much higher values) should be discussed. Additionally, there is evidence (e.g., policy statements by the National Institutes of Health and some regulatory bodies) that the methodology has a strong influence on results. The current document “tiptoes” around this reality; EPA needs to provide stronger statements about this, for example by stating that the methodology “does” as opposed to “may” have influence. The lack of strong acknowledgment of the limitations of fluoride analysis carries over into the McClure discussion later in the document, where these limitations are important. Finally, multiple studies recognize the large individual variation in the sources for water intake; this uncertainty is not well addressed.
- Dr. Fox referenced her written comments in response to this charge question (see page F-19 of Appendix F), in which she listed a series of questions, which she had made from the perspective of a risk assessor: “Does the available data overestimate, underestimate or both? Can the sources of uncertainty be prioritized? Are the different analytical methods contributing to more uncertainty than changes in diet? How does an understanding of the largest sources of uncertainty help us understand the data or help us characterize the analyses?” She felt that the uncertainty discussion would be much clearer if the document would address these questions. Agreeing with the prior comment on the role of methodological uncertainty, she recommended that the document more adequately characterize the methodological difficulties, and include any definitive quantitative information on uncertainty, whether leading to under- or overestimates.
- Dr. Abbott referenced her written comments in response to this charge question (see pages F-8 to F-9 of Appendix F). She emphasized that quantitative assessment of how influential the food intake studies were in calculating the RSC was both possible and important. She also questioned whether combining the 90th percentile value for drinking

water intake with all the other values would yield a valid estimate of total drinking water intake.

EPA Response: Dr. Donohue clarified that use of the 90th percentile value for drinking water intake and use of the average body weight were Agency policy. In response to a reviewer question, she agreed that a sensitivity analysis would improve understanding of the range of uncertainty around the data points selected for the analysis.

The reviewer responded that choosing one number was not erring on the side of being conservative; a sensitivity analysis would illuminate how the selected number compared with other possibilities that might be more protective of public health.

EPA Response: The EPA RSC analysis is governed by EPA policy rather than the methodologies employed by the researchers that provided the data. The experimental methodologies described in the text are those provided in the published studies that were used by EPA. The EPA policy limitations are acknowledged in the introduction and are now included in the preface as well. EPA has increased the discussion of uncertainty in response to the peer reviewer’s suggestions. The methodological variables inherent in the different critical studies are not included in the added text. However, the added text does demonstrate the impact of EPA study selection criteria on the outcome of the analysis.

As suggested by the peer reviewers, EPA has evaluated the impact of choosing a different data point as representative of specific media on the output from the analysis. It has also included information on the change that would result if there were an allowance for tooth brushing twice a day. There already was discussion of the confidence bounds around many of the averages selected as representative of the solid foods, beverages, and toothpaste intakes for the age groups in the peer review draft. The fact that average values were used in the analysis is a matter of EPA policy as are the use of the average drinking water F concentration and the 90th percentile drinking water intake. These limitations are now mentioned in several locations in the report.

The analysis of the dietary contribution of fluoride to exposure at the time of the Dean (1942) study (the basis of the RfD) was a confusing feature of the peer review draft of the exposure and RSC analysis. That analysis and the data that support it have been removed from the document and are now included as an appendix to the noncancer dose-response assessment. That analysis provides the dietary contribution for the RfD derivation based on the Dean (1942) drinking water concentration data. The peer reviewers were fully supportive of this change.

Charge Question 3. Please consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may have for alternative studies that you believe are more representative of exposures.

Reviewers held differing opinions about the adequacy of study descriptions and whether the selected studies were representative of exposures.

- Dr. Abbott referred EPA to the written comments she had provided in response to this question (see pages F-10 to F-11 of Appendix F) and asked that the Agency consider all these comments. She noted in particular that there appeared to be a mistake in the “0.5 to > 1 year” row of Table 6-1, since it seemed that the value for the addition of powdered formula should have been higher than stated. A complete explanation of this concern is provided in her written comments in response to Charge Question 7.²
- A reviewer recommended that the document provide more discussion about the quality of the literature on the various exposure assessment methodologies, including whether any methodologies are better suited than others for the analysis and how this factored into choosing the key studies.
- Dr. Martinez Mier said she found the selected studies to be representative and thought they would be recognized as valuable by others with dental expertise. She suggested that dental professionals with experience in this area would probably understand the studies, as described in the document, but she was concerned whether readers outside this area of expertise would be able to understand them. She felt that some studies that reflect more contemporary analytical methodologies should be included, and referred EPA to her written comments for more details on this comment and for suggested references (see pages F-26 to F-27 of Appendix F).
- Speaking from a soil and groundwater perspective, Dr. Ozsvath clarified that there is no database for fluoride in soils comparable to that used to analyze fluoride concentrations in public drinking water supplies. There are studies supporting a range, but there is no way to characterize those data statistically. He noted that a 2009 document prepared for

² This response reads as follows: “Table 6-1 states the overall mean from Ophaug (1985) (0.17 mg/d) was adjusted by subtracting the milk/formula intake from the earlier Ophaug study and then adding the 0.14 mg/d estimate from the powdered formula study by Van Winkle et al., 1995 using tap water to make the formula. This almost doubles the original Ophaug estimate and appears to be an incorrect combination of a fluoride concentration in food (Van Winkle et al. 1995) with an exposure estimate (Ophaug, 1985). To add the Van Winkle study to the Ophaug study, you would have to know how much formula was consumed in the Ophaug study. If the results from Van Winkle really are concentrations and are reported in mg/L (and not in mg/kg or some mass-mass basis) you would have to know the amount of liters of formula consumed in Ophaug to estimate the mg F/d contributed to the diet.”

Health Canada³ used 100 ppm as the average fluoride concentration in soil to estimate daily fluoride intake from soil ingestion, but this value might not apply to the U.S. He suggested that EPA provide more justification for its approach, including the use of water and soil data that do not have the same level of precision. A reviewer asked if this should be included in a sensitivity analysis. Dr. Ozsvath responded that the drinking water database is large enough to characterize probabilistically, so it is possible to know how the representative number relates to the whole database; however, this is not possible with the soil data.

EPA Response: The document discusses the strengths and weaknesses of the dietary methodologies for estimating populations and individual exposures (Section 2.5.1). However, the reviewer is correct in that there was no statement about which methods are best suited to the exposure and RSC analysis. A paragraph has been added at the end of Section 2.5.1 that provides the EPA’s opinion on which of the dietary methodologies were most appropriate for their analysis.

EPA examined the estimate for the formula fed children and did find an error which has been corrected. The revised value is lower than the original number by 0.01 mg.

Table 6-1 of the peer review draft explained the EPA calculation for formula fed children as follows:

- The Overall mean (0.17 mg/day) from 22 market baskets, and national food intake data (see Table 2-24), was the starting point for the calculation. The Ophaug et al. (1985) data apply to 6-month-old infants.
- The mean was adjusted by subtracting the milk/other dairy/formula intake of 0.06 mg/day from (Ophaug, 1980a Table 2-23) and replacing it with 0.14 mg/day from powdered formula (Van Winkle et al., 1995) [$0.17 \text{ mg/day} - 0.06 \text{ mg/day} + 0.14 \text{ mg/day} = 0.25 \text{ mg/day}$]. The Van Winkle intake from 1 L of formula was 14 mg. Children in the age range of interest drink 0.971 L/day. Thus, the formula contributed $0.14 \text{ mg/L} \times 0.971 \text{ L} = 0.136 \text{ mg}$ (rounded to 0.14 mg).
- The fluoride from the water added to reconstitute the formula is included in the drinking water compartment [$0.87 \text{ mg/L} \times 0.971 \text{ L} = 0.84477 \text{ mg}$ (rounded to 0.84 mg)].

The major reason why the value corrected to reflect children fed from reconstituted formula is higher than the Ophaug et al. (1985) value is because the Ophaug et al. number is based on a diet that includes both milk and formula intakes while the EPA number is based on a diet that replaces the milk and formula from Ophaug with formula prepared from powdered concentrate yielding a higher daily intake of fluoride (0.14 mg/day) than the milk and formula from Ophaug et al (1985) of 0.06 mg/day. Milk fluoride levels are low (0.02 mg/L; see Table 2-10) while the powdered formula results in a higher contribution to the formula as served (0.14 mg/L).

³ Federal-Provincial-Territorial Committee on Drinking Water. 2009. Fluoride in Drinking Water <http://fluoridealert.org/canada.2009.report.pdf>

Dr. Martines Mier submitted a list of studies of fluoride exposure for EPA’s consideration. These studies were evaluated by EPA; those that represented populations from outside of the United States were not considered suitable for inclusion in the exposure and RSC report.

EPA contacted Health Canada to discuss the basis for their 100 ppm soil estimate. They were not able to verify that the cited source was the origin for the number they used. The author of the Health Canada document indicated that she will inform EPA when she finds a good reference for a soil number.

Charge Question 4. Please comment on EPA’s rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically justified and clearly and objectively described? What changes or improvements would you suggest?

Dr. Martinez Mier noted that, in their written comments, all reviewers had recommended that EPA needed to provide further discussion on the selection of age groups. Reviewers had also provided several comments that the water and food exposure for infants appeared to be high and that the report needed to provide a better description of the variation in food concentrations. A number of reviewers also commented on the limited geographic area considered in the studies and the number of subjects involved in the studies. She briefly listed other individual written comments (see Appendix H) and then opened the floor for discussion.

- Dr. Abbott commented that EPA’s rationale for selection of the age groups selection was not clear, which made this portion of the document very confusing, particularly since the review document appeared to use different age groups than the underlying data. It was also puzzling why the draft RSC Analysis utilized historical data for this analysis since it seemed to her that calculations using more current data could have been made. She emphasized that this part of the document was very confusing and she referred EPA to all of her written comments in response to this question (see page F-11 in Appendix F).
- Dr. Fox commented that EPA should provide a better explanation of the criteria the Agency used to identify key data and studies and the considerations used to determine what was representative. She referred the Agency to her written comments for details (see page F-19 of Appendix F).
- Dr. Martinez Mier said she understood that use of data from the Dean study (1942) was necessary due to the lack of recent fluorosis prevalence data, but the RSC Analysis needed to better explain why those data elements were selected. She was particularly concerned that the dental community would question why EPA used the Dean (1942) data rather than more recent data. She recommended that EPA better clarify its rationale for including this study.
- A reviewer noted that while she understood the benchmark dose issue and that the Dose-Response Report determined the choice of Dean (1942) as the best study for addressing dose-response, she still questioned why EPA did not use current dietary exposure information in the RSC Analysis. It was unclear whether the RSC would be based on the Dean (1942) data or more recent data.

Noting their confusion about use of the Dean (1942) data, reviewers revisited the idea, proposed by Dr. Donohue during the Question 1 discussion, that EPA remove the description of the McClure (1943) data from the draft RSC Analysis and add it as an appendix to the Dose-Response Report. They agreed this was a good idea.

EPA Response: The data that were included in the exposure and RSC report for the purpose of estimating exposure at the time the critical study (Dean, 1942) was conducted was the source of

much of the confusion reported by the reviewers in response to this question. After the peer review meeting, EPA removed the early studies from the report and included them as an Appendix to the dose-response document. This enabled EPA to also remove the dose-response discussion in the exposure and RSC report that were linked to the application of the McClure data and contributed to the reviewer’s confusion. The reviewers accepted the EPA’s proposed approach to remedy the situation.

As a result of these changes all of the dose-response information that supports the EPA RfD is now in the appropriate document. EPA believes that this change removes the origin of most of the reviewers concerns expressed in their responses to the charge question.

EPA has added a statement to the preface which states the reason why the age groups were partitioned as they were. The criteria applied when selecting the critical studies to represent each age group were added to the introduction to Chapter 6 and the text dedicated to identifying the preferred study was expanded so that the reasons for not selecting a different representative study are provided in cases where it had not been included in the peer review draft. Chapter 7 provides information on RSC values that would had resulted from the use of a different critical study as part of the sensitivity analysis suggested by the peer reviewers.

Charge Question 5. Please comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication, as supported by the concentrations found in various food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940’s?

Reviewers noted that Charge Question 5 probably should have referred to McClure (1949)⁴ rather than (1943). All reviewers agreed that the report should better clarify the food intake estimates, especially in Table 2-25, where the McClure data are compared to more contemporary data.

Dr. Donohue clarified that the McClure food data were used to determine the dose-response and not the RSC.

Reviewers emphasized that EPA needed to add a forward in both the RSC Analysis and the Dose-Response Document to clarify the purpose of the two documents and their relationship to one another, since it cannot be assumed both documents will be read together.

Reviewers also recommended that discussion of adding 0.01 to get the POD be moved to the Dose-Response Report and that EPA clarify how the 0.5 ppm value was selected from the four values presented by McClure in the 1940s studies.

Dr. Donohue affirmed that, in response to reviewers’ comments, the Agency will move discussion of the McClure data to an appendix in the Dose-Response Report, and will respond to reviewers’ comments on that section even though it will be part of a different document. However, Dr. Donohue noted that EPA will need to keep some of the historical data in the RSC Analysis to show that the analytical methods have given different results (e.g., that values for fluoride in meat and poultry decreased over time since the 1940s as the analytical methods changed).

Additional reviewer comments included the following:

- A reviewer noted that the document did explain the importance of determining the food contribution, but the introduction was confusing, as was the section comparing the RfD (based on McClure data) and current RSC values.
- Another reviewer noted that, at one point in the draft RSC Analysis, the McClure data are considered a reasonable basis for estimations, but Table 2-25 states that the McClure results differ from current studies. The analytical limitations of the McClure study compromise the results, and this needs to be clearly stated in RSC Analysis

⁴ McClure, F.J. 1949. Fluoride in foods. Public Health Reports 64:No. 34, pp 1061–1074.

- Dr. Martinez Mier said she wanted to amend a sentence discussing fluoride concentrations in her pre-meeting comments to add the word “or higher” so that the sentence would read: “Interferences most likely resulted in reported fluoride concentration in foods lower **or higher** than actual concentrations.” She added that several reports in the dental literature have compared food and beverage and analysis of dental tissue where different methods have been used, and the interferences from these methods, particularly less sensitive methods, resulted in both higher and lower fluoride concentrations. This should be clarified the RSC Analysis.
- The approach for the food intake estimate is reasonable, but the need to estimate fluoride from 1940s food intake data, and the selection of 0.5 ppm from McClure (1943) as the estimate for fluoride in solid foods, is not clearly explained or supported. This explanation is very important and belongs up front in the purpose/problem statement. The discussion of Table 2-25 in the analysis offers possible explanations for why there are differences between McClure and more contemporary data, but the document should clarify how the differences inform the RSC Analysis.
- It is unclear why data from 1943 (McClure) are being used to set today’s RSC. The data seem irrelevant to the RSC Analysis. This needs to be clarified. There is a discrepancy between Table 2-12, which reports data from McClure (1949) and Table 2-25, which reports data from McClure (1943, 1949).
- Dr. Ozsvath referenced his written comments in response to this charge question, in which he noted a possible contradiction (see pages F-30 and F-31 of Appendix F). Specifically, on page 34 the authors state that the differences between McClure’s (1943, 1949) data and the more recent USDA (2005)⁵ data shown in Table 2-25 “cast doubt on the results of exposure assessments derived from some of the early food data.” However, in the third paragraph on page 122, the authors cite the same data (in Table 2-25) and state that “McClure’s (1943) estimate for dietary intake based on a diet where solid foods had an average of 0.5 ppm fluoride appears to provide a reasonable basis for the contribution of solid foods to total exposure in the 1940s.” Dr. Ozsvath noted that these statements appear to be contradictory, but that could perhaps be because the authors intended to cite Table 2-41, not 2-25 on page 122. This issue needs clarification.

EPA Response: As indicated in some of the prior responses and in the peer review report, the inclusion and application of the early dietary fluoride data was confusing to the peer reviewers. EPA internal reviewers had similar difficulties and it was clear to the EPA that the revisions that had been made based on the internal peer review comments had not resolved the problem.

EPA believes that their proposal to remove the early dietary data and place it in an appendix that would be added to the dose-response document is a good solution to the problem. The EPA suggestion was endorsed by the peer reviewers and has been executed.

In developing the Appendix for the dose-response document, EPA removed all dietary data published before 1980 unless there was a specific reason to retain it. In the new Appendix the EPA expanded the comparison between the analytical results from McClure (1943, 1949) and

⁵ USDA (U.S. Department of Agriculture). 2005. USDA National Fluoride Database of Selected Foods and Beverages, Release 2. Nutrient Data Laboratory, Agricultural Research Services, U.S. Department of Agriculture. Beltsville, MD.

those from the USDA (2005) fluoride database to include a much greater assortment of foods likely to have been part of the pre World War II diet.

The comparison of the early analytical results to the current values support the EPA conclusion that, for some food groups, the colorimetric analysis utilized by McClure led to fluoride concentration values that were high and that there was no biological reason why those food items would have higher levels of fluoride in 1930 to 1940 than they do now.

The more current fluoride concentration values for foods that had high fluoride concentrations in the McClure data set supported the selection of 0.5 ppm as a reasonable estimate for total dietary fluoride in solid foods during the 1930 to 1940, time period when the children in the Dean (1942) study were exposed.

It was mentioned by the peer reviewers that Health Canada used a different value for food in the era of the Dean (1942) study. EPA contacted Health Canada to identify the approach used. In one respect, the approach was similar to that used by EPA. The concentrations in foods from current analyses (Dabeka et al., 1995) were utilized in place of those from McClure. The Canadian approach differed from that used by the EPA because they based their value on an assumed 1940 era diet rather than the caloric allotments and average ppm concentrations in foods that were the basis of the McClure (1949) estimates used by EPA.

Charge Question 6. Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.

Dr. Donohue clarified that EPA had limited the RSC Analysis to studies from the U.S. and Canada initially, eventually eliminating many of the Canadian studies. Reviewers made the following comments:

- Dr. Abbott drew EPA’s attention to the dietary intake references she had included in her written comments (see page F-13 of Appendix F). She was unsure where they should be added. She said that, because the RSC Analysis included so much historical data, she had been unsure what type of references to provide.
- Dr. Martinez Mier referred EPA to the many references she had provided in her written comments (see pages F-22 to F-28 of Appendix F). She strongly recommended that EPA considering including studies from other countries and not just U.S. data when describing methodologies. For example, studies by Jackson, Dunipace, and Levy use more recent methodologies and not, for example, ashing, a method that has not been used in many years.
- Dr. Ozsvath suggested two references in his written comments that he recommended be added to the RSC Analysis (see page F-31 of Appendix F). The first reference (Beltran et al., 2002)⁶ is relevant to increases in fluorosis cases, a central focus of the RSC Analysis; this study addresses how fluorosis prevalence changed over time within populations exposed to drinking water with different fluoride content. The second reference (Federal-Provincial-Territorial Committee on Drinking Water, 2009)⁷ is significant (even though the RSC Analysis does not consider Canadian studies), because the Canadian equivalent found a very different RSC for drinking water. He suggested that EPA add an explanation of this difference to the RSC Analysis.

EPA Response: In response to the peer review comments, EPA did the following:

- Added the suggested studies that applied to the U.S. population.
- Requested information from Health Canada regarding the estimate of the 1930-1940 dietary fluoride level for children.

⁶ Beltran, E.D., S.O. Griffin, and S.A. Lockwood. 2002. Prevalence and trends in enamel fluorosis in the United States from the 1930s to the 1980s. *Journal of American Dental Association* 133(2):157-165.
<http://jada.ada.org/cgi/content/full/133/2/157>

⁷ Federal-Provincial-Territorial Committee on Drinking Water. 2009. Fluoride in Drinking Water
<http://fluoridealert.org/canada.2009.report.pdf>

- Expanded the discussion of the analytical methodologies used by Levy and Jackson as found in the published papers.

The Health Canada estimate for the exposure of children under age 12 during the 1930-1940 time period, when it is rounded to two decimal places, is the same value used by EPA (0.01 mg/kg/day) even though the approach differed (Table B-5 of the Canadian Report). This number is the Canadian value that applies to the situation where there is no fluoride in the drinking water supply.

In the Health Canada dietary study all foods and beverages were prepared with drinking water containing 1 mg/L water. The studies selected by the EPA either used distilled water for beverage preparation or water with considerably lower fluoride content. The Canadian dietary estimate for young children is similar to the EPA value. In the case of adults, the value is higher but use of water containing 1 mg/L for beverage preparation should account for some of that difference.

Charge Question 7. Please provide any additional comments and/or further suggestions you may have for improving the document.

Dr. Martinez Mier noted the wide variety of written comments reviewers had provided in response to this question. She read through the list summarizing these comments (see Appendix H) and invited discussion. Reviewers agreed that Section 8 of the document was confusing and that the draft RSC Analysis ends abruptly. They recommended that a concluding paragraph or section be added summarizing the outcomes and conclusions of the RSC Analysis. Discussion included the following comments:

- Dr. Abbott referenced her written comments in response to Charge Question 7 (see pages F-13 to F-18 of Appendix F). She noted that many of those comments also pertained to other charge questions, and clarified that she did not have additional comments.
- Dr. Martinez Mier commented that the dental literature has made an effort to distinguish between the terms “intake” and “exposure” for fluoride specifically. A document published by CDC on the safe use of fluoride provides definitions for these terms, one being systemic, the other topical. For fluoride via the oral route, “intake” pertains to ingestion, whereas “exposure” pertains to what is put in the mouth but not ingested. Toothpaste is an example of “exposure,” but toothpaste that is swallowed becomes “intake.” Dr. Martinez Mier recommended that EPA clarify its use of these terms. Another reviewer agreed that use of the term “intake” in the RSC Analysis was confusing; in particular, it was unclear whether it referred to fluoride intake or also connected with food consumption.
- In reference to p. 79 of the draft RSC Analysis, two reviewers suggested it would be useful to have an idea of how many children under 14 years of age are served by community water systems and potentially impacted by fluoride in these systems. This context should be added in one of the documents resulting from this process, perhaps the final management decision document. It may be possible to estimate this from NHANES data by using the survey weights to estimate how many children were exposed. Also, it would be important to look at actual beverage sources and not just assume that the liquid in all beverages came from the reported drinking water system. The CSFII provides a great amount of detail about beverage sources.
- Dr. Martinez Mier noted that there is some dental literature on the “halo effect,” which means that individuals who are not in a community with fluoridated drinking water can still be exposed to fluoride by consuming products made in other communities that do have fluoridated water. The literature does not quantify this amount, but mentions that it plays a role.
- A reviewer noted that water fluoridation is considered one of the top ten public health achievements in the last century, yet the draft RSC Analysis discusses potential health effects associated with this achievement. She thought it important to consider the potential public health implications associated with release of the RSC Analysis to the

extent that it could generate concern over fluoride in drinking water. Even though they are important, the public health benefits of drinking water fluoridation are not within the document’s scope. She wondered whether the document should specify what percentage of the population served by public water systems would potentially be affected by dental fluorosis. Dr. Donohue clarified that this issue is acknowledged in the Dose-Response Report and that, legally, EPA cannot endorse dental fluoridation.

- Section 8.2 (Estimates of Tolerable Upper Limit Exposures) is important, but very confusing as written and needs to be clarified. In particular, the use of the term “margin of exposure” in the draft RSC Analysis (see page 121) is potentially confusing to risk assessors, who use this term in a different way. The document should avoid, or at least clarify, terms such as this that can be construed differently by different specialists.
- Dr. Fox noted that interpretation of exposures over the RfD (as discussed on page 125) will inevitably vary; however, in assessments of anthropogenic chemicals (where exposures are involuntary and not nutritionally essential), interpretations vary across different parts of EPA, and increased risk is not proportionate to dose or exposure increases. She noted that she had provided EPA Office of Air definitions of “hazard index” and “hazard quotient” in her written comments (see page F-21 of Appendix F).
- Dr. Ozsvath emphasized that Table 8-2 and Figures 8-1 through 8-3 need clarification and re-wording and referred EPA to his written comments for details (see pages F-32 and F-33 of Appendix F).
- Noting a written comment that use of mixed units was confusing, a reviewer clarified that standardization of units, though desirable, may not always be possible, because the choice of units is often driven by the analytical method used. Conversion is not possible, for example, unless the specific homogenization process used by labs for each specific food is reported in the original study. Use of mixed units is to some degree an outcome of the lack of standardization of units in the food-fluoride literature. Another reviewer responded that conversion of beverage units from mg/L to mg/kg (the units used for food) may be possible by making an assumption about the specific gravity of the beverage.

This would inject another source of uncertainty, but would standardize the units, which would benefit comparison.

- A reviewer found it difficult to follow whether the document was discussing daily exposure (mg fluoride/day) or the amount of fluoride intake from food (mg fluoride/kg/day); the latter should not be used as representative of what people are eating because it is not clear what they have consumed. EPA should make clear that the document reports the units provided in the original study.

EPA Response: Several suggestions made by the peer reviewers were implemented during the post peer review revisions to the document as follows:

- All usages of the term intake and exposure were checked to make sure they were applied appropriately. EPA is in agreement that intake refers to what is actually ingested via the oral exposure route. However, in many cases EPA believes that “exposure” or “oral

exposure” is the appropriate term because the value presented was not a measurement of ingestion by a group of subjects in a controlled study, but an estimate of a population’s oral exposure made on the basis of what the general population is likely to have consumed in their diets, not necessarily what was consumed, swallowed and absorbed.

- The description of the IOM (1997) Tolerable Upper Intake Level was derived from the IOM publication. However it was revised in an attempt to strengthen the discussion without diverting from the IOM definition of the UL values. The term “margin of exposure” was removed from the document.
- EPA has attempted to clarify the fact that the beverage exposure values are not based on the assumption that the water in the beverage comes from the local public water system. In fact the opposite is true, EPA choose studies where reconstituted beverages were made with distilled deionized water if possible. If no study was available that met that condition, a study from a market basket collected in the area with the lowest fluoride concentration was chosen and the fluoride concentration in the water provided for the reader.
- EPA reworded the text associated with Table 8-1 and Figures 8-1 to 8-3.
- EPA added a more extensive summary and conclusion to chapter 8 than was in the peer review draft.

EPA did not make any changes to the units reported by the researchers in their published studies. Tables report the units [mg/L or mg/kg food, or mg/kg/day] as they were reported by the published papers. All EPA estimates in Chapter 8 are in units of mg/day.

The hazard index (HI) terminology is not generally used by the EPA OW and was not introduced into the document. The EPA authors feel that HI approach is more relevant to anthropogenic chemicals that lack benefit than to chemicals with established benefits at appropriate intakes.

EPA did not introduce any direct discussion of the halo effect into the document. The authors feel that the impact of the halo effect is captured in the studies that included commercial water. The only cases where tap water from the consumers tap is reflected in a beverage value were acknowledged, and the fluoride concentration of the tap water was provided.

EPA did not add any data on the number of children age 14 or younger that are served by public water systems. Those data are collected and utilized by the OGWDW during the second six-year review of the fluoride MCL. The data submitted by the states does not identify the population served by age categories. The dose-response document and this exposure and RSC document are resources that will be used in the process of evaluating whether or not the current MCLG and/or MCL will be revised.

The EPA dose-response and exposure reports do not negate the benefits associated with fluoridation. Those benefits are clearly evident in the dose-response analysis which also clearly demonstrates a leveling off of the benefit as fluoride levels in drinking water increase above the

fluoridation range. Given the current media that lead to fluoride intake by children, the challenge is to find the best approach to use for insuring that intakes do not exceed the levels that confer a lasting benefit.

The EPA monitoring data from public water systems clearly show that there are many public water systems that provide their customers with drinking water that routinely contains more than 1.2 mg/L fluoride. The EPA analysis was initiated to determine if there is a meaningful opportunity to reduce the risk of children in those systems from developing teeth with severe dental fluorosis.

The fact that the average fluoride levels from public water systems that report the detection of fluoride falls in the fluoridation range is a reflection of the number of systems nationwide that fluoridate their water supply.

Closing Discussion and Remarks

Dr. Donohue summarized the key messages the Agency had heard from reviewers during the meeting:

- A reader’s expertise affects how the RSC Analysis is read and understood. EPA should therefore provide more clarifications (e.g., of terminology, studies, etc.), so readers with a variety of backgrounds can better understand the document.
- Both the draft RSC Analysis and the Dose-Response Report currently lack an overview or roadmap. The Agency will add forwards to both documents that explain the “big picture.” The forward for the RSC Analysis will clearly:
 - State that the analysis relied exclusively on published studies from the U.S. for the dietary data. A few of the key studies for toothpaste ingestion and brushing frequency were Canadian.
 - Describe the limitations of the analysis
 - State the objectives of the analysis
 - Outline the critical steps in the analysis
 - Describe how the objectives were met
- EPA understands the reviewers’ concern about including a sensitivity analysis; however, a sensitivity analysis of a 0.02 to 0.03 mg/kg/day difference between beneficial and apparently adverse amounts of fluoride would likely simply show that the uncertainty values overlap. This makes it difficult to define where beneficial becomes adverse and adverse becomes beneficial. The Agency can look at how choosing a different study would affect the results of the RSC Analysis.
- Because people do not consume the same type or quantity of foods and beverages every day, any number in a consumption study will not be fully representative. Drinking water consumption is probably going to be more consistent than food consumption, but this is an inherent difficulty in dealing with essential nutrients and predicting how much people need or how much is too much. The Agency can try to improve the presentation in this

part of the report, but will always encounter that difficulty. Dietary risk assessment practices differ from toxicology risk assessment practices.

- EPA will use consistent terminology or at least recognize differences in terminology among disciplines.
- The Agency will rework the concluding section to describe what the next steps will be.
- EPA will move the discussion of the McClure data out of the RSC Analysis and into Dose-Response Report.

Reviewers agreed this was generally a good reflection of key points they had made⁸, and added the following comments and recommendations:

- The document needs to provide a clear justification for the selection of specific data sets and critical studies, perhaps in the forward/overview that EPA will be adding at the beginning of the RSC Analysis.

EPA Response: The text explaining the reasons for the selection of the key studies was expanded in the final report.

- The uncertainty discussion should be expanded.

EPA Response: The uncertainty discussion was expanded as suggested by the peer reviewers.

- In Table 7-2, EPA should use different values in the boxes representing fluoride intake from different sources to see how that affects the RSC.

EPA Response: EPA examined the impact of selecting alternative studies on the Total Exposure and RSC and reported the impact of the changes in the revised report.

- EPA should discuss how the characterization of beverages in a separate category from food affects the use of the estimates of indirect drinking water consumption implicitly included in the daily drinking water consumption reported in EPA’s 2004 document⁹ and how these estimates are used in the RSC calculation. The document should better clarify how the Pang (1992)¹⁰ data were used, in particular: What constitutes a store-bought beverage or a beverage prepared with de-ionized water? For example, is iced tea brewed in a restaurant or store considered store-bought? This matters because the drinking water figure from 2004 in the RSC Analysis includes indirect drinking water. However, beverages such as brewed iced tea, that are made from water in a store, provide another source of fluoride from community water supplies. In summary, EPA should clarify how the market basket approach relates to commercially purchased beverages and whether it could include any beverages that might have fluoride from a community water source.

⁸ In a post-meeting comment, Dr. Abbott noted that she did not agree that dietary risk assessment practices necessarily differ from toxicology risk assessment practices, especially when the chemical in question is being regulated as a contaminant and not as a dietary supplement.

⁹ U.S. EPA. 2004. Estimated Per Capita Water Ingestion and Body Weight in the United States – An Update. U.S. EPA, Washington, D.C.

¹⁰ Pang, D.T.Y., C.L. Phillips, and J.W. Bawden. 1992. Fluoride intake from beverage consumption in a sample of North Carolina children. *J. Dent. Res.* 71:1382–1388.

EPA Response: The Pang report did not provide the information to answer the question posed. EPA has reported the steps that were taken to minimize any impact of any indirect water that was included in the drinking water compartment of the total exposure section from being double counted. For most of the age categories all reconstituted beverages were prepared with distilled water. If there was no study where that was the case, EPA selected the data where the local water had the lowest fluoride concentration which was in all cases well below the average tap water concentration from public drinking water systems.

- A reviewer asked why beverage intake for infants was listed as zero in the draft RSC Analysis.

EPA Response: EPA clarified that the market basket survey defined “juice” as a “fruit.” The reviewer recommended that EPA clarify this in the document. EPA expanded the description of the liquids included in the beverage component of a market basket survey.

- Dr. Martinez Mier noted that the University of Minnesota has developed a software program to assess individual fluoride intake based on what, in an interview, an individual reports having eaten. The software uses mean fluoride values from peer-reviewed laboratory analysis, so could be helpful to EPA as a source of data on mean values of fluoride in various types of food. Values are added to the database on an ongoing basis as new data become available. Dr. Martinez Mier agreed to send a reference for this database to EPA.¹¹

EPA Response: Dr. Martinez Mier provided a link to the database to EPA. However, it was not used for the Exposure RSC report because the EPA report is based on the findings of peer reviewed published studies.

- A reviewer suggested that EPA examine the USDA fluoride database to see what it might yield in terms of current consumption values and to get an idea of how much uncertainty was associated with relying on older studies with few groups of foods versus data available in the current USDA database.¹²

EPA Response: EPA used the fluoride data from the USDA database in order to gauge the accuracy of some of the published data and provides a number of Tables based on that data in Section 2 of the Exposure and RSC report.

- A reviewer suggested that the document add the uncertainties associated with the likely future increase of fluoride in food due to increased use of fluoridated water in preparing food products.

¹¹ After the meeting, Dr. Martinez Mier sent the following links to this database and software:

<http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/Fluoride/F02.pdf>

<http://www.ncc.umn.edu/products/databasenutrientsratioscomponents.html>

¹² In a post-meeting comment, this reviewer added that EPA should investigate using current fluoride concentration in food data from the USDA’s fluoride database in combination with more recent consumption data (from the CSFII or NHANES databases) to provide a quantitative estimate of the difference between the values from the older studies and a more current exposure estimate, at least for those food groups where both types of concentration data exist. This could be accomplished by using a modeling approach like that used by EPA’s Office of Pesticide Programs for sulfuryl fluoride (use of the DEEM model and use of historical concentration data versus more current concentration data).

EPA Response: The EPA hypothesizes that the increase in the number of localities that fluoridate is responsible for the increased fluoride in commercial beverages and foods. Data on the mean fluoride concentrations in carbonated beverages, tea, and fruit flavored drinks are used to support the EPA hypothesis.

- A table such as Table 7-2 could be incorporated into a sensitivity analysis to get an idea of which of the numbers that have been estimated are most critical. Lacking that analysis, it is hard to have perspective on how sensitive some of the possible changes in values the reviewers have discussed will be to the RSC. For example, the document ignores the amount of fluoride in the atmosphere and this is probably appropriate. The importance of the soil intake is not certain, but it may be relatively low compared to food.

EPA Response: The revised report included expanded discussion of the relative contribution of the media quantified to total exposure. The impact of selection of alternatives to the key studies was also added to the revised document.

Final Note: All editorial comments made by the reviewers were addressed by EPA.

IV. EXTERNAL PEER REVIEW REPORT

**Summary Report of the Meeting to
Peer Review EPA’s Draft Document
*Fluoride: Exposure and Relative Source Contribution
Analysis***

Arlington, VA
May 14, 2010

Submitted to:
Office of Water
U.S. Environmental Protection Agency (EPA)
Washington, DC 20460

Submitted by:
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Final Report: July 28, 2010

Notice

This report was prepared by Eastern Research Group, Inc. (ERG), a U.S. Environmental Protection Agency (EPA) contractor, as a general record of discussion during the Peer Review Meeting on EPA’s draft document *Fluoride: Exposure and Relative Source Contribution Analysis*, held May 14, 2010, in Arlington, Virginia. This report captures the main points and highlights of the meeting. It is not a complete record of all details discussed, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Statements represent the individual views of meeting participants.

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Appendix A: Peer Reviewers

Appendix B: Charge to Peer Reviewers

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Appendix D: Meeting Agenda

Appendix E: Meeting Observers

Appendix F: Reviewer Post-Meeting Comments

Appendix G: EPA Slides Presented at the Peer Review Meeting

Appendix H: Panel Chair’s Summary of Reviewer Pre-Meeting Comments

1. Introduction

As part of a series of activities, described below, to evaluate the drinking water standards for fluoride, the U.S. Environmental Protection Agency (EPA) conducted a relative source contribution analysis of fluoride in drinking water and developed the draft document, *Fluoride: Exposure and Relative Source Contribution Analysis* (RSC Analysis). This report summarizes discussion at a workshop, held in Arlington, Virginia, on May 14, 2010, to peer review the draft RSC Analysis.

Background

EPA established the current drinking water standards for fluoride in 1986. The Maximum Contaminant Level Goal (MCLG) and the Maximum Contaminant Level (MCL) were set at 4.0 milligrams per liter (mg/L) of water to protect against stage three skeletal fluorosis, a disorder characterized by calcification of ligaments, immobility, muscle wasting, and neurological problems related to spinal cord compression. Exposure to fluoride from other sources, including food, beverages, dental products, supplements, industrial emissions, pharmaceuticals, and pesticides, was not considered at that time. EPA also established a non-enforceable secondary standard (the Secondary Maximum Contaminant Level, or SMCL) of 2.0 mg/L to protect against moderate/severe dental fluorosis (considered a cosmetic effect at the time). The MCLG/MCL were set assuming all exposure to fluoride would come from drinking water—a 100% relative source contribution (RSC).

The 1996 Safe Drinking Water Act Amendments require 6-year reviews of drinking water contaminant standards. EPA performed the first such review of the fluoride standards in 2002-2003. The Agency concluded that no revision was appropriate at that time because it had asked the National Academies of Science (NAS) National Research Council (NRC) to evaluate the health effects and occurrence of fluoride in public water supplies and to examine the current standards considering new data published after the 1986 regulation and a 1993 NRC review of fluoride that EPA had also requested. Fluoride would be reexamined during the next 6-year review.

In response to this charge, the NRC released a March 2006 report, *Fluoride in Drinking Water: A Scientific Review of EPA’s Standards*¹³, and concluded that the current MCLG of 4.0 mg/L does not adequately protect against severe dental fluorosis. The report also recommended that EPA update the dose-response assessment for severe dental fluorosis, consider susceptible populations, characterize uncertainty and variability, and update exposure assessment (i.e., the RSC). In response to these recommendations, EPA developed a three-part action plan, which included: 1) conducting a dose-response analysis for severe dental fluorosis and skeletal effects; 2) examining the relative source contribution of fluoride in drinking water; and 3) studying the relationship of fluoride to cancer.

The first part of the action plan was addressed with the development and March 2008 peer review of a report on *Dose-Response Analysis for Severe Dental Fluorosis and Skeletal Effects* (Dose-Response Report). This document established a point of departure (POD) for severe dental fluorosis, but was unable to complete a dose-response analysis of the skeletal effects of fluorosis due to inadequate data. EPA will initiate the third part of the action plan, examining the relationship of fluoride to cancer, once an ongoing study, recommended by the NRC as a starting point, is

¹³ NRC (National Research Council). 2006. *Fluoride in Drinking Water. A Scientific Review of EPA’s Standards*. Washington, DC: National Academy Press.

published. Development, peer review, and finalization of *Fluoride: Exposure and Relative Source Contribution Analysis* (RSC Analysis) constitute the second part of the action plan. This report summarizes the results of the peer review of the draft RSC Analysis.

Development of the Draft RSC Analysis

EPA prepared the draft RSC Analysis in order to determine current fluoride exposures, as well as exposures at the time (1930s-1940s) when the dose-response data used for the 1986 SMCL were collected. The SMCL is based on severe dental fluorosis and is non-enforceable, but does require public notification when the average fluoride concentration in drinking water from a public drinking water system exceeds 2 mg/L in order to alert families of the risk for severe dental fluorosis in children.

Calculation of the health-based MCLG for non-cancer endpoints generally requires application of an RSC to adjust for sources of exposure other than drinking water that are not reflected in the POD for MCLG derivation. In the case of fluoride, the endpoint of concern was identified by the NRC (2006) as severe dental fluorosis, characterized as displaying confluent pitting in the enamel of at least two permanent teeth. EPA selected Dean (1942)¹⁴ as the critical study and used the 95th percentile lower bound concentration in drinking water associated with a 0.5% prevalence of severe dental fluorosis in that study as their POD.

The draft RSC Analysis report uses data published in the peer-reviewed literature to estimate dietary fluoride in the 1930s-1940s, as well as current total exposures from plain (direct and indirect) drinking water; solid foods; commercial beverages; toothpaste; soils; and use of the recently registered pesticide, sulfuryl fluoride. The recent exposure data are used to determine the current relative source contribution of fluoride in drinking water to total exposure for the 90th percentile drinking water intake, in accordance with EPA policy.

The draft RSC Analysis was internally peer-reviewed by representatives from EPA’s Office of Children’s Health, Office of Congressional and Intergovernmental Relations, and Office of Research and Development. That review was completed in January 2010.

2010 External Peer Review

In spring 2010, Eastern Research Group, Inc. (ERG), an EPA contractor, organized an independent peer review of the draft RSC Analysis to assess its scientific quality and utility. Four experts (Appendix A) conducted this review:

- Linda C. Abbott, U.S. Department of Agriculture
- Mary A. Fox, John Hopkins Bloomberg School of Public Health
- E. Angeles Martinez Mier, Indiana University School of Dentistry
- David L. Ozsvath, University of Wisconsin-Stevens Point

¹⁴ Dean, H.T. 1942. The investigation of physiological effects by the epidemiology method. In: *Fluoride and Dental Health*. Publ. Amer. Assoc. Advanc. Sci., no. 19. pp 23–31.

ERG provided the reviewers with the draft RSC Analysis and a charge (Appendix B), which asked for reviewer comments on the various aspects of the document.

In the first stage of the review, the experts worked individually to prepare individual written pre-meeting comments. To kick off this stage of the review, ERG organized and facilitated a conference call in which EPA presented background on the context for developing the document (see slides in Appendix C) and reviewers were invited to ask questions of clarification to understand the context for the review and the charge questions. (The background provided on this call is summarized in the “Background” section, above.) Reviewers then prepared and submitted their pre-meeting comments, hereafter referred to as “written comments,” which ERG then provided to all reviewers and EPA prior to the meeting.

In the second stage, ERG convened a one-day peer review meeting, on May 14, 2010, in Arlington, Virginia. Appendix D provides the meeting agenda and Appendix E provides the list of meeting observers. After the meeting, ERG prepared a draft summary report of the proceedings. Reviewers were asked to check the report for accuracy and completeness, and also to submit post-meeting comments by amending their pre-meeting comments in light of the discussions. Reviewers post-meeting comments are included as Appendix F.

This report summarizes the meeting proceedings as follows:

- Section 2 presents ERG and EPA opening remarks.
- Section 3 summarizes the reviewers’ discussions organized by charge question.
- The appendices provide the list of peer reviewers (Appendix A), charge to peer reviewers (Appendix B), EPA slides presented during the background teleconference (Appendix C), the meeting agenda (Appendix D), meeting observers (Appendix E), reviewer post-meeting comments (Appendix F), EPA slides presented at the beginning of the peer review meeting (Appendix G), and Dr. Martinez Mier’s summary of reviewer pre-meeting comments (Appendix H).

2. Opening Remarks

ERG Remarks

Jan Connery (ERG), the meeting facilitator, opened the meeting by welcoming the reviewers and asking the reviewers and EPA document authors to introduce themselves. Ms. Connery reviewed the meeting agenda (Appendix D). She noted that the pre-meeting comments were developed by reviewers working individually prior to the meeting, and that reviewers may express different opinions during the meeting. Ms. Connery made clear that all discussions were to be among reviewers only; however, reviewers could request, and EPA could offer, clarifications where relevant.

Ms. Connery then introduced Eric Burneson, Chief of the Targeting & Analysis Branch, Standards and Risk Management Division, EPA Office of Ground Water and Drinking Water, and Joyce Donohue from EPA’s Office of Water (OW), to provide opening remarks. Dr. Donohue served as a co-author of the draft RSC Analysis.

EPA Remarks

Mr. Burneson welcomed the reviewers and thanked them for their participation. He noted the purpose and importance of the review to EPA as part of the RSC Analysis development process, and provided brief background on the fluoride drinking water standard. He emphasized that the RSC Analysis would inform future decision-making by OW’s Standards and Risk Management Division, particularly concerning the future review and potential revision of the national primary drinking water regulation for fluoride. EPA is required to review the drinking water standards at least every 6 years, and has recently concluded its most recent round of national primary drinking water standard reviews. However, the Agency may initiate a review and rulemaking at any time when the science suggests there is a meaningful opportunity for public health protection by revising a drinking water standard. This peer review is an important part of the process to ensure that EPA has the best available science assembled for decision-making with respect to the fluoride drinking water regulation.

Dr. Donohue then summarized the history of the fluoride drinking water standards, the 2006 recommendations by NRC, and the results of those recommendations (see slides in Appendix G). When EPA completed its first 6-year review of the fluoride drinking water standard in 2003, the Agency asked the National Academy of Sciences to examine the hazards associated with fluoride in drinking water and the relative sources of exposure to fluoride in light of new data since the NAS’ prior review in the 1990s. The resulting 2006 NRC report¹⁵ recommended that EPA conduct a dose-response analysis for several dental fluorosis, which the NAS for the first time considered to be an adverse health effect (as opposed to a cosmetic effect) because data indicated increased susceptibility to cavities as a result of pitting and thinning of enamel. The NRC also asked EPA to do a dose-response analysis for skeletal effects, including skeletal fluorosis and fractures. They recommended an extended assessment of exposure to sensitive populations, including children

¹⁵ NRC (National Research Council). 2006. Fluoride in Drinking Water. A Scientific Review of EPA’s Standards. Washington, DC: National Academy Press.

during the period of tooth formation and adults for skeletal effects. NAS recognized that the issue of whether fluoride causes osteosarcomas is highly controversial and recommended that EPA wait until the results of an ongoing study at Harvard University were published to make a decision on this issue. The Agency intends to prepare a report on this potential effect once the Harvard study is published.

EPA developed a draft Dose-Response Report, which was externally peer-reviewed in March 2008. The reviewers agreed that the Agency chose the correct critical study, but suggested that EPA model to the 0.5 percent level, if possible, rather than the 1 percent level in the report. The Agency did model to the 0.5 percent level, and that changed the point of departure for the critical endpoint from 2.1 mg/L to 1.87 mg/L.

EPA began to develop the RSC Analysis after the March 2008 peer review. An initial draft of the analysis was internally reviewed within EPA during the past year and then revised in response to internal comments. The resulting draft is the one the current external reviewers received to review.

Dr. Donohue described the key steps that would follow this external peer review, including revising the RSC Analysis in response to reviewer comments and posting the revised document simultaneously with Dose-Response Report on the Internet. At that point, EPA's Office of Ground Water and Drinking Water will consider whether to revise the fluoride MCLG and/or MCL, which are currently both 4.0 mg/L based on severe skeletal fluorosis. Any revision of the standards should maintain or improve health protection, but the cost of achieving the revised standard must be justified by the health benefits of doing so.

Dr. Donohue then explained the differences between the MCL and MCLG, as well as EPA's general policies in calculating the MCLG. The MCLG, which is not enforceable, will be based on the NRC report as the description of hazard and dose-response assessment. The MCL, which is enforceable, considers not only human health data but also analytical and technological limitations, as well as the cost involved in requiring compliance. She noted that it is difficult to remove fluoride from water.

In response to a reviewer's question, Dr. Donohue confirmed that the MCL applies only to public water systems (including non-transient, non-community systems) and that EPA has no regulatory authority over private water supplies, including wells, cisterns, and bottled water. The reviewer pointed out that the RSC would need to include consideration of the contribution that populations served by public water systems would also receive from water sources other than public water systems.

Dr. Donohue then described how EPA generally approaches developing the MCLG. First EPA determines a Reference Dose (one of the outputs from the Dose-Response Report). The Agency uses the Reference Dose (RfD) to calculate the Drinking Water Equivalent Level (DWEL), which assumes that the total exposure comes from drinking water. EPA determines the DWEL by multiplying the RfD by the weight of the sensitive population (this could be done for each age group identified), and then dividing by the drinking water intake. The Agency uses OW's 2004 survey of individual food intake, in part to stay consistent with the age groupings the Agency has been using. EPA then calculates an MCLG, protective for populations served by public water systems, by multiplying the DWEL by the RSC. Dr. Donohue explained that the Agency cannot use its subtraction option because of the tolerances for pesticides containing fluoride. When another office within EPA has a regulation governing a contaminant, EPA policy requires that a percentage

approach be used. EPA policy is to use average body weight and the 90th percentile drinking water intake when determining the RSC.

In the case of fluoride, the 1.87 mg/L from the benchmark dose analysis could be used as the point of departure to which an RSC would be applied in order to avoid the uncertainties involved in converting the concentration to dose (mg/kg/day) using body weight and water intake estimates that would apply to the 1930s-1940s time period when the exposures from the critical study occurred. These are options, but no decisions have been made about what approach will be used. Each age group could be used independently by applying its RSC to develop age-specific MCLGs and select the limiting value, or the Agency could normalize across the 0.5- to 14-year age range that is susceptible to severe dental fluorosis and get one value. EPA will be considering these options when the Office of Water considers potential changes to the MCLG after the RSC Analysis is finalized.

Dr. Donohue shared EPA’s assessment of findings in the draft RSC Analysis and the Dose-Response Report. In the draft RSC Analysis, the exposure estimate indicates that the fluoride RfD is being exceeded for some public water system consumer age groups at an average fluoride concentration of 0.87 mg/L. The prevalence of dental fluorosis has increased from approximately 10 percent (at the time of the critical study) to 23 percent in 1986-87, to 32 percent in 2000; unpublished data from CDC in 2004 show another substantial increase (based on the unpublished National Health and Nutrition Examination Surveys [NHANES] data).

The dose-response data considered by NAS are supportive of an increased risk of cavities when dental fluorosis is severe. Dental fluorosis, once acquired, cannot be reversed; the consequences are lifelong. Cavities meet the definition of an adverse health effect, especially when untreated, and the Agency cannot assume all cavities are treated. Over 4,000 public water systems in the U.S. deliver water supplies with naturally occurring fluoride at average concentrations above 0.87 mg/L. Most of these systems are groundwater systems, and many are small.

Dr. Donohue then shared the results of the Iowa Fluoride Study conducted by Dr. Steven Levy. The study involved 622 children of moderate to high socioeconomic status. Intakes of water, beverages, selected food supplements, and toothpaste were reported by the parents at 3- to 4-month intervals from birth to 48 months. When the children’s teeth were examined between ages 8 and 10, eight cases of severe fluorosis were detected. The study used a different scale from the Dean (1942) study¹⁶, and did not limit the severe designation only to cases where there was pitting of the enamel. Therefore, EPA asked Dr. Levy to provide information on whether any of the eight severe cases exhibited pitting. Photographs of seven of the severe fluorosis cases (photographs for the eighth case could not be located) showed that one of the seven children had pits in the enamel of the affected teeth. This child’s average intake from 9 to 36 months was 0.075 mg/kg/day. The larger data set showed no severe cases of dental fluorosis when exposure was equal to or less than 0.06 mg/kg/day. Dr. Donohue noted that EPA and the Centers for Disease Control (CDC) had agreed to work together to more thoroughly evaluate the drinking water concentrations that may have been associated with cases of severe dental fluorosis identified in recent data collections from the NHANES.

Discussion Notes

¹⁶ Dean, H.T. 1942. The investigation of physiological effects by the epidemiology method. In: *Fluoride and Dental Health*. Publ. Amer. Assoc. Advanc. Sci., no. 19. pp 23–31.

Ms. Connery thanked Dr. Donohue for her opening remarks and turned the meeting over to E. Angeles Martinez Mier, the panel chair, to begin the reviewer discussions. Dr. Martinez Mier had developed a powerpoint presentation (Appendix H) summarizing the reviewers’ pre-meeting comments for each charge question, which she displayed when initiating the consideration of each charge question to remind reviewers of their preliminary comments.

Early in the discussion, one of the reviewers, Linda Abbott, read a statement¹⁷ she had prepared and asked that it be included in this report. She said she had provided as many comments as she could in the time available for the review, and was concerned there could be additional issues in the document she would not have had time to identify. Other reviewers commented that they nevertheless found Dr. Abbott’s comments very valuable. Ms. Connery asked Dr. Abbott whether she would have time after the report to add comments she had not had a chance to make earlier, and Dr. Abbott replied that her ongoing job responsibilities would preclude that possibility.

Also during subsequent discussion, two reviewers noted that they had interpreted the requirement not to make copies of the report during the review as meaning they should not print a copy of the report. They reviewed the document on screen, but having a print version would have been helpful.

¹⁷“I originally declined the request to participate in this peer review. My schedule precluded me from devoting more than 20 hours to the project and I thought that was insufficient time to conduct a comprehensive review of the scientific information supporting the determination of a maximum contaminant level or maximum contaminant level goal. The letter of commitment estimates the level of effort for this task to be 28 to 30 hours including the eight-hour workshop. I estimate that I have already spent over 30 hours reviewing the document prior to the workshop. Even 30 hours was not an adequate amount of time to review such a complex document that relies so heavily on historical exposure levels, especially given the added effort to obtain the underlying references. Thus my assessment of the document should not be considered to be complete – there may be issues that I was unable to identify due to lack of time. The absence of comments on the use of an exposure assessment method, dataset or historical study should not necessarily be interpreted as agreement with the peer review draft.”

3. Reviewer Discussion

Charge Question 1: Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.

Reviewers noted agreement in their written comments that the purpose of the draft RSC Analysis was not clearly stated and that adding an overview or “road map,” including a statement of objectives, in the introductory section of the document would help address this concern.

Dr. Donohue noted that the Agency agreed with these pre-meeting comments, and had decided to add forwards to both the RSC Analysis and the Dose-Response Report in order to outline the study objectives and present a road map. She said that EPA planned to post both documents on the Internet at the same time. Dr. Donohue also noted that the external peer reviewers, as well as EPA internal reviewers, had clearly indicated confusion around presentation of how the Agency used the McClure (1943)¹⁸ data to estimate food contributions in 1942. She proposed that EPA would remove the description of the McClure (1943) data from the draft RSC Analysis and add it as an appendix to the Dose-Response Report. This seemed appropriate since those data are used in the Dose-Response Report rather than the RSC Analysis. She asked reviewers for feedback on whether they thought this change would address their concern about this section of the report.

Reviewers supported the idea of a forward and agreed to talk about the best location for the McClure (1943) data when they discussed Charge Question 5.

Dr. Ozsvath remarked that it was difficult to determine what the critical steps of the analysis were and why they were taken. He had alluded to this concern in his written response to Question 1 and elaborated on it in his response to Question 7 (see Appendix F). He noted that this concern was also echoed in Dr. Abbott’s detailed written comments. He recommended that the document include a road map, a list of objectives, and a statement at the end of the document clarifying how the objectives were met.

Dr. Martinez Mier noted that some of the terminology was not consistently used throughout the document. Also, some of the steps in the fluoride analysis are not consistent with those found in the current dental literature for fluoride analysis. Though the document is not intended for the dental community, it will inevitably be circulated within that community because it impacts dental fluorosis and caries prevention. Dr. Martinez Mier referred EPA to her written response to Charge Question 1 (see Appendix F) for specific suggestions about reorganizing the discussion of analytical methods and changing how things are referenced in order to bring the discussion more in line with contemporary analytical approaches used by the dental community.

Dr. Fox said she agreed with recommendations to improve clarity and transparency by stating the questions the document will address and the approach EPA used to address those questions. She also had concerns about the discussion of public health implications in Chapter 8. She had provided a detailed comment about this in her written response to Charge Question 7 and noted that she would talk about this in detail when Question 7 was discussed.

¹⁸ McClure, F.J. 1943. Ingestion of fluoride and dental caries. Quantitative relations based on food and water requirements of children 1-12 years old. *Amer. J. Dis. Child.* 66:362. [Republished in Publication 825, U.S. Public Health Service, 1962].

Dr. Abbott referenced all of her written comments in response to Charge Question 1 (see pages F-6 to F-8 of Appendix F). She also noted one additional comment. She recommended that, at the beginning of the document, EPA acknowledge the spectrum of populations obtaining drinking water from the full variety of sources, including community water supplies, spring water, bottled water, and well water, and clarify whether these sources factor into the MCL. The document seems to combine these at different levels in the RSC calculation because food intake is considered across the population as a whole, not just in those who drink community water. This is a particular problem when considering beverages. For example, beverages prepared by adding water and made away from home, like tea or beverages made from dry powders with extra indirect water, may not come from the same water supply used at home. In the Continuing Survey of Food Intakes by Individuals (CSFII), all these different types of water sources are associated with the different types of food and beverages. The document should acknowledge from the outset that the analysis combines these different populations for different parts of the estimate. Without this acknowledgment, readers will be confused when they learn that the document only considers populations served by community water systems and not those who are not served by those systems but who are exposed to fluoride in their diet by ingesting food or beverages made with fluoridated water (e.g., at a processing plant).

In response to this comment, Dr. Donohue clarified that EPA used data from the Food and Drug Administration’s (FDA’s) total diet study, which clearly identified in the market basket which beverages were made from public water and which at home. In the analysis, EPA subtracted out the portion of beverages made with public water. Dr. Abbott responded that the CSFII would provide a more refined estimate of the source of indirect water used in beverage preparation. Dr. Donohue clarified that EPA relied on the published literature for the RSC Analysis and did not conduct any independent analyses. In light of that clarification, a reviewer suggested that EPA state at the beginning of the document that the Agency had not conducted any new analyses and instead had relied exclusively on the literature. Other reviewers agreed it was important for EPA to more clearly explain what they did and did not do in the analysis.

Charge Question 2: Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.

Reviewers agreed that the document should provide a better discussion of uncertainty. Individual comments included:

- The draft RSC Analysis describes sources of uncertainty, but does not attempt to show how the RSC would be affected if different assumptions were made. A sensitivity analysis would help show how different assumptions would affect the RSC. Page 113 of the draft document states that the Agency believes these are reasonable estimates, but the Agency does not justify this statement; this part needs more scientific rigor.
- The draft RSC Analysis recognizes some sources of uncertainty (e.g., “technological limitations”), but should be more explicit in discussing the uncertainties associated with specific values from various studies related to fluoride analysis. The fact that uncertainty in fluoride analysis can go either way (leading to much lower or much higher values) should be

discussed. Additionally, there is evidence (e.g., policy statements by the National Institutes of Health and some regulatory bodies) that the methodology has a strong influence on results. The current document “tiptoes” around this reality; EPA needs to provide stronger statements about this, for example by stating that the methodology “does” as opposed to “may” have influence. The lack of strong acknowledgment of the limitations of fluoride analysis carries over into the McClure discussion later in the document, where these limitations are important. Finally, multiple studies recognize the large individual variation in the sources for water intake; this uncertainty is not well addressed.

- Dr. Fox referenced her written comments in response to this charge question (see page F-19 of Appendix F), in which she listed a series of questions, which she had made from the perspective of a risk assessor: “Does the available data overestimate, underestimate or both? Can the sources of uncertainty be prioritized? Are the different analytical methods contributing to more uncertainty than changes in diet? How does an understanding of the largest sources of uncertainty help us understand the data or help us characterize the analyses?” She felt that the uncertainty discussion would be much clearer if the document would address these questions. Agreeing with the prior comment on the role of methodological uncertainty, she recommended that the document more adequately characterize the methodological difficulties, and include any definitive quantitative information on uncertainty, whether leading to under- or overestimates.
- Dr. Abbott referenced her written comments in response to this charge question (see pages F-8 to F-9 of Appendix F). She emphasized that quantitative assessment of how influential the food intake studies were in calculating the RSC was both possible and important. She also questioned whether combining the 90th percentile value for drinking water intake with all the other values would yield a valid estimate of total drinking water intake.

Dr. Donohue clarified that use of the 90th percentile value for drinking water intake and use of the average body weight were Agency policy. In response to a reviewer question, she agreed that a sensitivity analysis would improve understanding of the range of uncertainty around the data points selected for the analysis. The reviewer responded that choosing one number was not erring on the side of being conservative; a sensitivity analysis would illuminate how the selected number compared with other possibilities that might be more protective of public health.

Charge Question 3: Please consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may for alternative studies that you believe are more representative of exposures.

Reviewers held differing opinions about the adequacy of study descriptions and whether the selected studies were representative of exposures.

- Dr. Abbott referred EPA to the written comments she had provided in response to this question (see pages F-10 to F-11 of Appendix F) and asked that the Agency consider all these comments. She noted in particular that there appeared to be a mistake in the “0.5 to > 1 year” row of Table 6-1, since it seemed that the value for the addition of powdered formula should have been higher than stated. A complete explanation of this concern is provided in her written comments in response to Charge Question 7.¹⁹
- A reviewer recommended that the document provide more discussion about the quality of the literature on the various exposure assessment methodologies, including whether any methodologies are better suited than others for the analysis and how this factored into choosing the key studies.
- Dr. Martinez Mier said she found the selected studies to be representative and thought they would be recognized as valuable by others with dental expertise. She suggested that dental professionals with experience in this area would probably understand the studies, as described in the document, but she was concerned whether readers outside this area of expertise would be able to understand them. She felt that some studies that reflect more contemporary analytical methodologies should be included, and referred EPA to her written comments for more details on this comment and for suggested references (see pages F-26 to F-27 of Appendix F).
- Speaking from a soil and groundwater perspective, Dr. Ozsvath clarified that there is no database for fluoride in soils comparable to that used to analyze fluoride concentrations in public drinking water supplies. There are studies supporting a range, but there is no way to characterize those data statistically. He noted that a 2009 document prepared for Health Canada²⁰ used 100 ppm as the average fluoride concentration in soil to estimate daily fluoride intake from soil ingestion, but this value might not apply to the U.S. He suggested that EPA provide more justification for its approach, including the use of water and soil data that do not have the same level of precision. A reviewer asked if this should

¹⁹ This response reads as follows: “Table 6-1 states the overall mean from Ophaug (1985) (0.17 mg/d) was adjusted by subtracting the milk/formula intake from the earlier Ophaug study and then adding the 0.14 mg/d estimate from the powdered formula study by Van Winkle et al., 1995 using tap water to make the formula. This almost doubles the original Ophaug estimate and appears to be an incorrect combination of a fluoride concentration in food (Van Winkle et al. 1995) with an exposure estimate (Ophaug, 1985). To add the Van Winkle study to the Ophaug study, you would have to know how much formula was consumed in the Ophaug study. If the results from Van Winkle really are concentrations and are reported in mg/L (and not in mg/kg or some mass-mass basis) you would have to know the amount of liters of formula consumed in Ophaug to estimate the mg F/d contributed to the diet.”

²⁰ Federal-Provincial-Territorial Committee on Drinking Water. 2009. Fluoride in Drinking Water <http://fluoridealert.org/canada.2009.report.pdf>

be included in a sensitivity analysis. Dr. Ozsvath responded that the drinking water database is large enough to characterize probabilistically, so it is possible to know how the representative number relates to the whole database; however, this is not possible with the soil data.

Charge Question 4: Please comment on EPA’s rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically justified and clearly and objectively described? What changes or improvements would you suggest?

Dr. Martinez Mier noted that, in their written comments, all reviewers had recommended that EPA needed to provide further discussion on the selection of age groups. Reviewers had also provided several comments that the water and food exposure for infants appeared to be high and that the report needed to provide a better description of the variation in food concentrations. A number of reviewers also commented on the limited geographic area considered in the studies and the number of subjects involved in the studies. She briefly listed other individual written comments (see Appendix H) and then opened the floor for discussion.

- Dr. Abbott commented that EPA’s rationale for selection of the age groups selection was not clear, which made this portion of the document very confusing, particularly since the review document appeared to use different age groups than the underlying data. It was also puzzling why the draft RSC Analysis utilized historical data for this analysis since it seemed to her that calculations using more current data could have been made. She emphasized that this part of the document was very confusing and she referred EPA to all of her written comments in response to this question (see page F-11 in Appendix F).
- Dr. Fox commented that EPA should provide a better explanation of the criteria the Agency used to identify key data and studies and the considerations used to determine what was representative. She referred the Agency to her written comments for details (see page F-19 of Appendix F).
- Dr. Martinez Mier said she understood that use of data from the Dean study (1942) was necessary due to the lack of recent fluorosis prevalence data, but the RSC Analysis needed to better explain why those data elements were selected. She was particularly concerned that the dental community would question why EPA used the Dean (1942) data rather than more recent data. She recommended that EPA better clarify its rationale for including this study.
- A reviewer noted that while she understood the benchmark dose issue and that the Dose-Response Report determined the choice of Dean (1942) as the best study for addressing dose-response, she still questioned why EPA did not use current dietary exposure information in the RSC Analysis. It was unclear whether the RSC would be based on the Dean (1942) data or more recent data.

Noting their confusion about use of the Dean (1942) data, reviewers revisited the idea, proposed by Dr. Donohue during the Question 1 discussion, that EPA remove the description of the McClure (1943) data from the draft RSC Analysis and add it as an appendix to the Dose-Response Report. They agreed this was a good idea.

Charge Question 5: Please comment on the validity of basing the food intake estimate for the 1940s on the McClure (1943) publication, as supported by the concentrations found in various

food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940s?

Reviewers noted that Charge Question 5 probably should have referred to McClure (1949)²¹ rather than (1943). All reviewers agreed that the report should better clarify the food intake estimates, especially in Table 2-25, where the McClure data are compared to more contemporary data. Dr. Donohue clarified that the McClure food data were used to determine the dose-response and not the RSC. Reviewers emphasized that EPA needed to add a forward in both the RSC Analysis and the Dose-Response Document to clarify the purpose of the two documents and their relationship to one another, since it cannot be assumed both documents will be read together.

Reviewers also recommended that discussion of adding 0.01 to get the POD be moved to the Dose-Response Report and that EPA clarify how the 0.5 ppm value was selected from the four values presented by McClure in the 1940s studies. Dr. Donohue affirmed that, in response to reviewers’ comments, the Agency will move discussion of the McClure data to an appendix in the Dose-Response Report, and will respond to reviewers’ comments on that section even though it will be part of a different document. However, Dr. Donohue noted that EPA will need to keep some of the historical data in the RSC Analysis to show that the analytical methods have given different results (e.g., that values for fluoride in meat and poultry decreased over time since the 1940s as the analytical methods changed).

Additional reviewer comments included the following:

- A reviewer noted that the document did explain the importance of determining the food contribution, but the introduction was confusing, as was the section comparing the RfD (based on McClure data) and current RSC values.
- Another reviewer noted that, at one point in the draft RSC Analysis, the McClure data are considered a reasonable basis for estimations, but Table 2-25 states that the McClure results differ from current studies. The analytical limitations of the McClure study compromise the results, and this needs to be clearly stated in RSC Analysis
- Dr. Martinez Mier said she wanted to amend a sentence discussing fluoride concentrations in her pre-meeting comments to add the word “or higher” so that the sentence would read: “Interferences most likely resulted in reported fluoride concentration in foods lower **or higher** than actual concentrations.” She added that several reports in the dental literature have compared food and beverage and analysis of dental tissue where different methods have been used, and the interferences from these methods, particularly less sensitive methods, resulted in both higher and lower fluoride concentrations. This should be clarified the RSC Analysis.
- The approach for the food intake estimate is reasonable, but the need to estimate fluoride from 1940s food intake data, and the selection of 0.5 ppm from McClure (1943) as the estimate for fluoride in solid foods, is not clearly explained or supported. This explanation is very important and belongs up front in the purpose/problem statement. The discussion of Table 2-25 in the analysis offers possible explanations for why there are differences between McClure and more contemporary data, but the document should clarify how the differences inform the RSC Analysis.

²¹ McClure, F.J. 1949. Fluoride in foods. Public Health Reports 64:No. 34, pp 1061–1074.

- It is unclear why data from 1943 (McClure) are being used to set today’s RSC. The data seem irrelevant to the RSC Analysis. This needs to be clarified. There is a discrepancy between Table 2-12, which reports data from McClure (1949) and Table 2-25, which reports data from McClure (1943, 1949).
- Dr. Ozsvath referenced his written comments in response to this charge question, in which he noted a possible contradiction (see pages F-30 and F-31 of Appendix F). Specifically, on page 34 the authors state that the differences between McClure’s (1943, 1949) data and the more recent USDA (2005)²² data shown in Table 2-25 “cast doubt on the results of exposure assessments derived from some of the early food data.” However, in the third paragraph on page 122, the authors cite the same data (in Table 2-25) and state that “McClure’s (1943) estimate for dietary intake based on a diet where solid foods had an average of 0.5 ppm fluoride appears to provide a reasonable basis for the contribution of solid foods to total exposure in the 1940s.” Dr. Ozsvath noted that these statements appear to be contradictory, but that could perhaps be because the authors intended to cite Table 2-41, not 2-25 on page 122. This issue needs clarification.

Charge Question 6: Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.

Dr. Donohue clarified that EPA had limited the RSC Analysis to studies from the U.S. and Canada initially, eventually eliminating many of the Canadian studies. Reviewers made the following comments:

- Dr. Abbott drew EPA’s attention to the dietary intake references she had included in her written comments (see page F-13 of Appendix F). She was unsure where they should be added. She said that, because the RSC Analysis included so much historical data, she had been unsure what type of references to provide.
- Dr. Martinez Mier referred EPA to the many references she had provided in her written comments (see pages F-22 to F-28 of Appendix F). She strongly recommended that EPA considering including studies from other countries and not just U.S. data when describing methodologies. For example, studies by Jackson, Dunipace, and Levy use more recent methodologies and not, for example, ashing, a method that has not been used in many years.
- Dr. Ozsvath suggested three references in his written comments that he recommended be added to the RSC Analysis (see page F-31 of Appendix F). The first reference (Beltran et al., 2002)²³ is relevant to increases in fluorosis cases, a central focus of the RSC Analysis; this study addresses how fluorosis prevalence changed over time within populations exposed to drinking water with different fluoride content. The second reference (Federal-Provincial-

²² USDA (U.S. Department of Agriculture). 2005. USDA National Fluoride Database of Selected Foods and Beverages, Release 2. Nutrient Data Laboratory, Agricultural Research Services, U.S. Department of Agriculture. Beltsville, MD.

²³ Beltran, E.D., S.O. Griffin, and S.A. Lockwood. 2002. Prevalence and trends in enamel fluorosis in the United States from the 1930s to the 1980s. *Journal of American Dental Association* 133(2):157-165.

<http://jada.ada.org/cgi/content/full/133/2/157>

Territorial Committee on Drinking Water, 2009)²⁴ is significant (even though the RSC Analysis does not consider Canadian studies), because the Canadian equivalent found a very different RSC for drinking water. He suggested that EPA add an explanation of this difference to the RSC Analysis.

Charge Question 7: Please provide any additional comments and/or further suggestions you may have for improving the document.

Dr. Martinez Mier noted the wide variety of written comments reviewers had provided in response to this question. She read through the list summarizing these comments (see Appendix H) and invited discussion. Reviewers agreed that Section 8 of the document was confusing and that the draft RSC Analysis ends abruptly. They recommended that a concluding paragraph or section be added summarizing the outcomes and conclusions of the RSC Analysis. Discussion included the following comments:

- Dr. Abbott referenced her written comments in response to Charge Question 7 (see pages F-13 to F-18 of Appendix F). She noted that many of those comments also pertained to other charge questions, and clarified that she did not have additional comments.
- Dr. Martinez Mier commented that the dental literature has made an effort to distinguish between the terms “intake” and “exposure” for fluoride specifically. A document published by CDC on the safe use of fluoride provides definitions for these terms, one being systemic, the other topical. For fluoride via the oral route, “intake” pertains to ingestion, whereas “exposure” pertains to what is put in the mouth but not ingested. Toothpaste is an example of “exposure,” but toothpaste that is swallowed becomes “intake.” Dr. Martinez Mier recommended that EPA clarify its use of these terms. Another reviewer agreed that use of the term “intake” in the RSC Analysis was confusing; in particular, it was unclear whether it referred to fluoride intake or also connected with food consumption.
- In reference to p. 79 of the draft RSC Analysis, two reviewers suggested it would be useful to have an idea of how many children under 14 years of age are served by community water systems and potentially impacted by fluoride in these systems. This context should be added in one of the documents resulting from this process, perhaps the final management decision document. It may be possible to estimate this from NHANES data by using the survey weights to estimate how many children were exposed. Also, it would be important to look at actual beverage sources and not just assume that the liquid in all beverages came from the reported drinking water system. The CSFII provides a great amount of detail about beverage sources.
- Dr. Martinez Mier noted that there is some dental literature on the “halo effect,” which means that individuals who are not in a community with fluoridated drinking water can still be exposed to fluoride by consuming products made in other communities that do have fluoridated water. The literature does not quantify this amount, but mentions that it plays a role.

²⁴ Federal-Provincial-Territorial Committee on Drinking Water. 2009. Fluoride in Drinking Water <http://fluoridealert.org/canada.2009.report.pdf>

- A reviewer noted that water fluoridation is considered one of the top ten public health achievements in the last century, yet the draft RSC Analysis discusses potential health effects associated with this achievement. She thought it important to consider the potential public health implications associated with release of the RSC Analysis to the extent that it could generate concern over fluoride in drinking water. Even though they are important, the public health benefits of drinking water fluoridation are not within the document’s scope. She wondered whether the document should specify what percentage of the population served by public water systems would potentially be affected by dental fluorosis. Dr. Donohue clarified that this issue is acknowledged in the Dose-Response Report and that, legally, EPA cannot endorse dental fluoridation.
- Section 8.2 (Estimates of Tolerable Upper Limit Exposures) is important, but very confusing as written and needs to be clarified. In particular, the use of the term “margin of exposure” in the draft RSC Analysis (see page 121) is potentially confusing to risk assessors, who use this term in a different way. The document should avoid, or at least clarify, terms such as this that can be construed differently by different specialists.
- Dr. Fox noted that interpretation of exposures over the RfD (as discussed on page 125) will inevitably vary; however, in assessments of anthropogenic chemicals (where exposures are involuntary and not nutritionally essential), interpretations vary across different parts of EPA, and increased risk is not proportionate to dose or exposure increases. She noted that she had provided EPA Office of Air definitions of “hazard index” and “hazard quotient” in her written comments (see page F-21 of Appendix F).
- Dr. Ozsvath emphasized that Table 8-2 and Figures 8-1 through 8-3 need clarification and rewording and referred EPA to his written comments for details (see pages F-32 and F-33 of Appendix F).
- Noting a written comment that use of mixed units was confusing, a reviewer clarified that standardization of units, though desirable, may not always be possible, because the choice of units is often driven by the analytical method used. Conversion is not possible, for example, unless the specific homogenization process used by labs for each specific food is reported in the original study. Use of mixed units is to some degree an outcome of the lack of standardization of units in the food-fluoride literature. Another reviewer responded that conversion of beverage units from mg/L to mg/kg (the units used for food) may be possible by making an assumption about the specific gravity of the beverage.

This would inject another source of uncertainty, but would standardize the units, which would benefit comparison.
- A reviewer found it difficult to follow whether the document was discussing daily exposure (mg fluoride/day) or the amount of fluoride intake from food (mg fluoride/kg/day); the latter should not be used as representative of what people are eating because it is not clear what they have consumed. EPA should make clear that the document reports the units provided in the original study.

Closing Discussion and Remarks

Dr. Donohue summarized the key messages the Agency had heard from reviewers during the meeting:

- A reader’s expertise affects how the RSC Analysis is read and understood. EPA should therefore provide more clarifications (e.g., of terminology, studies, etc.), so readers with a variety of backgrounds can better understand the document.
- Both the draft RSC Analysis and the Dose-Response Report currently lack an overview or roadmap. The Agency will add forwards to both documents that explain the “big picture.” The forward for the RSC Analysis will clearly:
 - State that the analysis relied exclusively on published studies from the U.S.
 - Describe the limitations of the analysis
 - State the objectives of the analysis
 - Outline the critical steps in the analysis
 - Describe how the objectives were met
- EPA understands the reviewers’ concern about including a sensitivity analysis; however, a sensitivity analysis of a 0.02 to 0.03 mg/kg/day difference between beneficial and apparently adverse amounts of fluoride would likely simply show that the uncertainty values overlap. This makes it difficult to define where beneficial becomes adverse and adverse becomes beneficial. But the Agency can look at how choosing a different study would affect the results of the RSC Analysis.
- Because people do not consume the same type or quantity of foods and beverages every day, any number in a consumption study will not be fully representative. Drinking water consumption is probably going to be more consistent than food consumption, but this is an inherent difficulty in dealing with essential nutrients and predicting how much people need or how much is too much. The Agency can try to improve the presentation in this part of the report, but will always encounter that difficulty. Dietary risk assessment practices differ from toxicology risk assessment practices.
- EPA will use consistent terminology or at least recognize differences in terminology among disciplines.
- The Agency will rework the concluding section to describe what the next steps will be.
- EPA will move the discussion McClure data out of the RSC Analysis and into Dose-Response Report.

Reviewers agreed this was generally a good reflection of key points they had made²⁵, and added the following comments and recommendations:

- The document needs to provide a clear justification for the selection of specific data sets and critical studies, perhaps in the forward/overview that EPA will be adding at the beginning of the RSC Analysis.
- The uncertainty discussion should be expanded.

²⁵ In a post-meeting comment, Dr. Abbott noted that she did not agree that dietary risk assessment practices necessarily differ from toxicology risk assessment practices, especially when the chemical in question is being regulated as a contaminant and not as a dietary supplement.

- In Table 7-2, EPA should use different values in the boxes representing fluoride intake from different sources to see how that affects the RSC.
- EPA should discuss how the characterization of beverages in a separate category from food affects the use of the estimates of indirect drinking water consumption implicitly included in the daily drinking water consumption reported in EPA’s 2004 document²⁶ and how these estimates are used in the RSC calculation. The document should better clarify how the Pang (1992)²⁷ data were used, in particular: What constitutes a store-bought beverage or a beverage prepared with de-ionized water? For example, is iced tea brewed in a restaurant or store considered store-bought? This matters because the drinking water figure from 2004 in the RSC Analysis includes indirect drinking water. However, beverages such as brewed iced tea, that are made from water in a store, provide another source of fluoride from community water supplies. In summary, EPA should clarify how the market basket approach relates to commercially purchased beverages and whether it could include any beverages that might have fluoride from a community water source.
- A reviewer asked why beverage intake for infants was listed as zero in the draft RSC Analysis. EPA clarified that the market basket survey defined “juice” as a “fruit.” The reviewer recommended that EPA clarify this in the document.
- Dr. Martinez Mier noted that the University of Minnesota has developed a software program to assess individual fluoride intake based on what, in an interview, an individual reports having eaten. The software uses mean fluoride values from peer-reviewed laboratory analysis, so could be helpful to EPA as a source of data on mean values of fluoride in various types of food. Values are added to the database on an ongoing basis as new data become available. Dr. Martinez Mier agreed to send a reference for this database to EPA.²⁸
- A reviewer suggested that EPA examine the USDA fluoride database to see what it might yield in terms of current consumption values and to get an idea of how much uncertainty was associated with relying on older studies with few groups of foods versus data available in the current USDA database.²⁹
- A reviewer suggested that the document add the uncertainties associated with the likely future increase of fluoride in food due to increased used of fluoridated water in preparing food products.
- A table such as Table 7-2 could be incorporated into a sensitivity analysis to get an idea of which of the numbers that have been estimated are most critical. Lacking that analysis, it is hard to have perspective on how sensitive some of the possible changes in values the

²⁶ U.S. EPA. 2004. Estimated Per Capita Water Ingestion and Body Weight in the United States – An Update. U.S. EPA, Washington, D.C.

²⁷ Pang, D.T.Y., C.L. Phillips, and J.W. Bawden. 1992. Fluoride intake from beverage consumption in a sample of North Carolina children. *J. Dent. Res.* 71:1382–1388.

²⁸ After the meeting, Dr. Martinez Mier send the following links to this database and software:

www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/Fluoride/F02.pdf
<http://www.ncc.umn.edu/products/databasenutrientsratioscomponents.html>

²⁹ In a post-meeting comment, this reviewer added that EPA should investigate using current fluoride concentration in food data from the USDA’s fluoride database in combination with more recent consumption data (from the CSFII or NHANES databases) to provide a quantitative estimate of the difference between the values from the older studies and a more current exposure estimate, at least for those food groups where both types of concentration data exist. This could be accomplished by using a modeling approach like that used by EPA’s Office of Pesticide Programs for sulfurlyl fluoride (use of the DEEM model and use of historical concentration data versus more current concentration data).

reviewers have discussed will be to the RSC. For example, the document ignores the amount of fluoride in the atmosphere and this is probably appropriate. The importance of the soil intake is not certain, but it may be relatively low compared to food.

Ms. Connery noted that reviewers would receive a copy of the draft summary report to check for accuracy and completeness before it was finalized. She thanked the reviewers for their participation. Dr. Donohue thanked reviewers for the diversity of their comments, noting that they had opened the Agency’s eyes to different perspectives and that had been very valuable.

Appendix A: Peer Reviewers



Peer Review Workshop of EPA’s Draft Document Fluoride: Exposure and Relative Source Contribution Analysis

Navy League Building
Arlington, VA
May 14, 2010

Reviewers

Linda C. Abbott, Ph.D.

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Appendix B: Charge to Peer Reviewers

Technical Charge to External Peer Reviewers

Fluoride Exposure and Relative Source Contribution Analysis

BACKGROUND

Calculation of the health-based Maximum Contaminant Level Goal (MCLG) for noncancer endpoints generally requires application of a Relative Source Contribution (RSC) to adjust for sources of exposure other than drinking water that are not reflected in the Point of Departure (POD) for the MCLG derivation. In the case of fluoride, the POD is a drinking water concentration from 1942 for a 0.5% incidence of severe dental fluorosis, characterized as displaying confluent pitting in the enamel of at least two permanent teeth.

This document uses data published in the peer-reviewed literature to estimate dietary fluoride in the 1940's as well as current total exposures from plain (direct and indirect) drinking water, solid foods, beverages, toothpaste, and soils. The recent exposure data are used to determine the current relative source contribution of fluoride in drinking water to total exposure for the 90th percentile drinking water intake (EPA policy).

CHARGE QUESTIONS

1. Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.
2. Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.
3. Please consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may for alternative studies that you believe are more representative of exposures.
4. Please comment on EPA's rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically justified and clearly and objectively described? What changes or improvements would you suggest?
5. Please comment on the validity of basing the food intake estimate for the 1940's on the McClure (1943) publication, as supported by the concentrations found in various food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940's?
6. Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.

7. Please provide any additional comments and/or further suggestions you may have for improving the document.

**Appendix C:
EPA Slides Presented
During Teleconference**

Exposure and Relative Source Contribution for Fluoride

Document Background
Peer Reviewer Presentation
April 20, 2010

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1

Regulatory History for Fluoride

- **1986 - Existing Drinking Water Standards**
 - Established MCLG /MCL of 4.0 mg/L to protect against crippling (stage 3) skeletal fluorosis
 - Assumed all exposure comes from drinking water (i.e., a 100% relative source contribution or RSC*)
 - Set Secondary MCL (SMCL) at 2.0 mg/L to protect against objectionable (moderate/severe) dental fluorosis (then considered a cosmetic effect)
- **2003 – Finalized “first” review of drinking water standards**
 - No revision appropriate at that time; requested National Academies of Science National Research Council (NRC) to examine current standards in the light of new data since 1986 regulation and a 1993 NRC report
- **2010 – Finalized “second” review of drinking water standards**
 - Revisions to MCLG and MCL will be considered when the ongoing dose-response and relative source contribution assessments are complete

*Note: As the exposure sources from other media increase, the RSC value for drinking water decreases. This lowers the MCLG. The current MCLG assumes a 100% RCS for drinking water.

Six Year Review of Fluoride Regulations (2002/2003)

- Required by the 1996 Safe Drinking Water Act Amendments
- Reviewed new scientific data related to the fluoride MCLG and MCL and identified:
 - Many studies of the effects of fluoride on bone published after the EPA-requested 1993 NRC review of fluoride
 - Comprehensive recent reviews by WHO, England (2), ATSDR
 - Institute of Medicine (IOM) dietary intake guidelines and tolerable upper limit values (2001)
- EPA recommended fluoride for a comprehensive review by NRC

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3

NRC Charge and the 2006 Report

- **2003 EPA Charge to NRC**
 - Review recent health/sources of exposure data; Evaluate basis for MCLG/MCL and SMCL; Advise EPA on adequacy of MCL and SMCL to protect children and others from adverse effects; and identify data gaps/research needs
- **March 2006 NRC Report**
 - **Dental Fluorosis** - Most panel members concluded “severe dental fluorosis” is an adverse effect (due to thinning/pitting of the tooth enamel which increases the risk for cavities); MCL does not adequately protect against this effect
 - **Skeletal/Bone effects** - MCL may not protect against bone fractures
 - **Other Effects** - Human and animal data limited on endocrine and neurodevelopmental effects; research needed
 - **Cancer** – Evidence tentative and mixed (most studies look at bone cancer); Wait for publication of two Harvard osteosarcoma (bone cancer) studies*
 - **Advice to EPA** - update the dose-response assessment, consider susceptible populations, characterize uncertainties/variability, and update the exposure assessment (i.e., the relative source contribution)

*These studies were expected in 2006 but only one has been published thus far.

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4

NRC (2006) Caries Conclusions

- Severe dental fluorosis is characterized by discrete and confluent pitting which constitutes enamel loss
- Severe enamel fluorosis compromises the health protective function of enamel and is consistent with the prevailing risk assessment definition of an adverse health effect
 - “Severe enamel fluorosis may increase carries risk by reducing the thickness of the protective enamel layer and by allowing food and plaque to become entrapped in the enamel defects”
- Data from 11 out of 14 comparisons of degree of fluorosis with cavity incidence support the hypothesis that severe enamel fluorosis is associated with an elevated incidence of cavities when compared to lower levels of fluorosis

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5

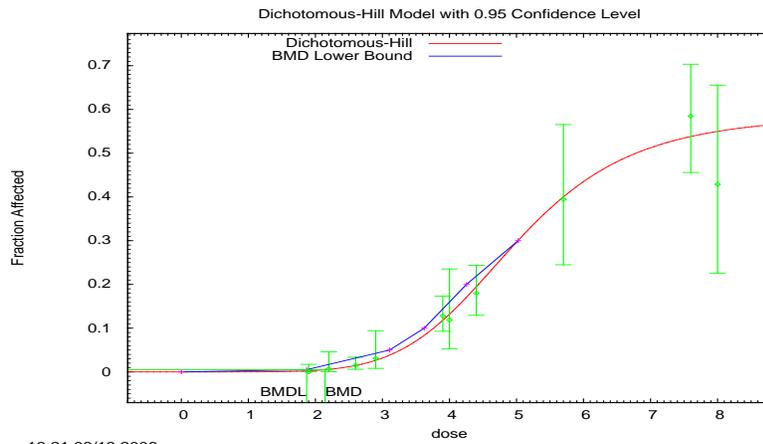
U.S. EPA Action Plan

- Three Documents
- Dose-Response Analysis for Severe Dental Fluorosis and Skeletal Effects
 - Fluoride in Drinking Water (NRC, 2006) provides hazard identification
 - Peer reviewed - March 2008
 - Post Peer Review Document completed
 - Establishes a point of departure for severe dental fluorosis of 1.87 mg/L F
 - Inadequate data to support a dose-response analysis of the skeletal effects.
 - Protection against severe dental fluorosis likely to be protective for skeletal effects
- Relative Source Contribution
 - U.S. EPA internal review completed in January 2010
 - Peer Review May 14, 2010
- Relationship of Fluoride to Cancer
 - To be initiated after publication of Harvard study by Douglas as recommended by NRC (2006) – Study not yet published

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6

Benchmark Modeling of the Dean Data

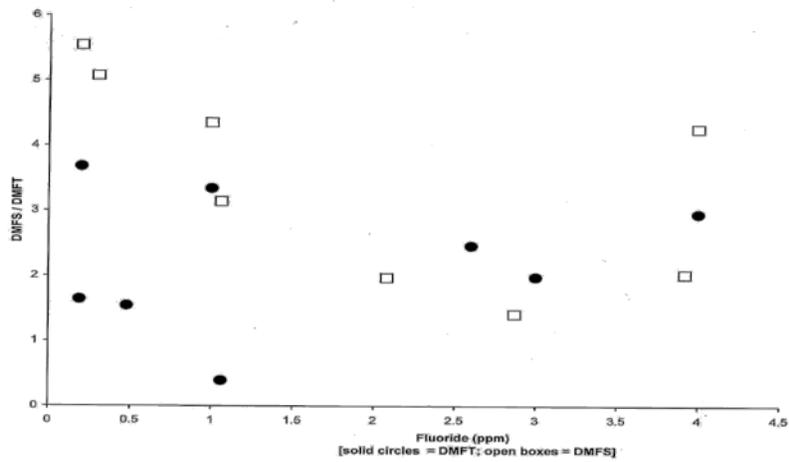


Revised from 1% based on peer review recommendations.

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7

Fluoride Concentration vs. DMFT /DMFS



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8

EPA Analysis of the Fluoride Concentration and Cavity Prevalence Relationship

- Data provide some support for the hypothesis that the enamel defects in severe dental fluorosis increase the prevalence of cavities compared to those with mild to moderate fluorosis
 - Differences are minimal in some cases
- Cavity prevalence where there is no or minimal exposure to fluoride is greater than that found in concert with severe dental fluorosis.
- School age children with drinking water concentrations of ≥ 4 ppm F had a higher cavity prevalence than those in systems with 2 ppm F but a lower prevalence than those in systems with 1 ppm F.
 - The cavity data are not suitable for dose response modeling
- EPA analysis identified the increase in cavities as the adverse health effects and used the dose-response for severe dental fluorosis as a surrogate for the cavities

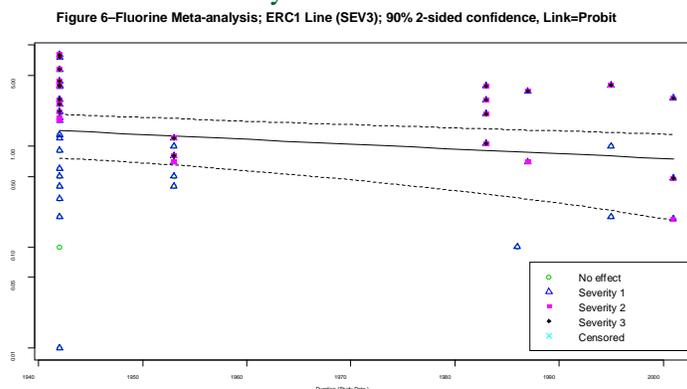
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9

Changes in Fluoride Exposure: 1940 vs. 2010

- There are many sources of exposure to fluoride that did not exist at the time of the Dean (1942) analysis
 - Artificially fluoridated water
 - Commercial baby formula (powdered and concentrate)
 - Fluoridated toothpastes and mouthwashes
 - Sulfuryl fluoride pesticide (registered 2004)
- Dental fluorosis has increased
 - 1940: ~ 10%
 - 1987: 23%
 - 1999-2002: 32%
 - Comparable data for severe dental fluorosis are not available

Categorical Regression Analysis with Date of Study as the Variable



Data demonstrate that the water concentration associated with a 1% increase in severe dental fluorosis decreases with the date of the study. This is supportive of the conclusion that other sources of exposure have increased.

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11

Importance of the RSC

- The RSC is applied to the Point of Departure for severe dental fluorosis to identify the MCLG
- The lower the RSC, the lower the MCLG
 - Dental fluorosis only develops during pre-eruptive tooth formation
 - 0.5 years to 14 years is the period of vulnerability for permanent teeth
 - Includes development of third molars (wisdom teeth)

Appendix D: Meeting Agenda



Peer Review Workshop of EPA’s Draft Document Fluoride: Exposure and Relative Source Contribution Analysis

Navy League Building
Arlington, VA
May 14, 2010

Agenda

- 8:00 a.m. Registration/Check-in
- 8:30 a.m. **Welcome, Introductions, Meeting Purpose & Agenda** *Jan Connery, ERG*
- 8:40 a.m. **EPA Welcome Remarks***Eric Burneson, Chief, Targeting & Analysis Branch, EPA/OW*
- 8:45 a.m. **Background Presentation***Joyce Donohue, EPA/OW*
- 9:05 a.m. **Reviewer Discussions** *E. Angeles Martinez Mier (Chair) & Panel*
- 1) Describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.**
- 9:25 a.m. **2) Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.**
- 10:00 a.m. BREAK
- 10:15 a.m. **3) Please consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may for alternative studies that you believe are more representative of exposures.**
- 10:50 a.m. **4) Please comment on EPA’s rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically**

justified and clearly and objectively described? What changes or improvements would you suggest?

Agenda (cont.)

- 11:30 a.m. **5) Please comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication, as supported by the concentrations found in various food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940’s?**
- 12:15 p.m. LUNCH
- 1:15 p.m. **6) Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.**
- 1:30 p.m. **7) Please provide any additional comments and/or further suggestions you may have for improving the document.**
- 2:00 p.m. BREAK
- 2:15 p.m. **Reviewer Conclusions & Recommendations.....** *E. Angeles Martinez Mier (Chair) & Panel*
- 3:45 p.m. **Closing Remarks** *Jan Connery & EPA/OW*
- 4:00 p.m. ADJOURN

Appendix E: Meeting Observers



Peer Review Workshop of EPA’s Draft Document Fluoride: Exposure and Relative Source Contribution Analysis

Navy League Building
Arlington, VA
May 14, 2010

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Appendix F: Reviewer Post-Meeting Comments

Reviewer Biographies

Linda C. Abbott, Ph.D.

Regulatory Risk Analyst
Office of Risk Assessment and Cost-Benefit Analysis
U.S. Department of Agriculture

Dr. Linda Abbott is a risk assessment modeler with USDA’s Office of Risk Assessment and Cost-Benefit Analysis (ORACBA) where she reviews regulatory risk assessments, provides advice on risk assessments and collaborates with other USDA agencies to identify areas where risk assessment could produce valuable information for regulatory decision makers. She reviews and provides guidance on human health risk assessments, dietary exposure assessments, and ecological risk assessments on conservation practices, agricultural chemicals and invasive species. She is also interested in the risks and benefits associated with agricultural nanotechnology applications and recently served on the Joint Food Agriculture Organization – World Health Organization Expert Meeting on Application of Nanotechnologies in the Food and Agriculture Sectors: Potential Food Safety Implications. She served as a Food Quality Protection Act Science Review Member of the Environmental Protection Agency’s Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel on Selected Issues Associated with the Risk Assessment Process for Pesticides with Persistent, Bioaccumulative and Toxic Characteristics. Prior to joining ORACBA, Dr. Abbott was an ecologist at USDA’s Animal and Plant Health Inspection Service, where she conducted ecological risk assessments on the application of chemical or biological pesticides and analyzed the environmental impacts of various APHIS programs involving the introduction of biocontrol agents, exclusion of foreign animal diseases and plant pests, and eradication or suppression of introduced pests or disease. Dr. Abbott has a Ph.D. in Biology-Ecology from Utah State University.

Mary A. Fox, Ph.D.

Assistant Professor
Department of Health Policy and Management
Johns Hopkins Bloomberg School of Public Health

Dr. Mary Fox is Assistant Professor in the Department of Health Policy and Management at the Johns Hopkins Bloomberg School of Public Health. She teaches Methods in Quantitative Risk Assessment featuring probabilistic exposure assessment methods for the Johns Hopkins Risk Sciences and Public Policy Institute’s Certificate Program. Dr. Fox’s research is focused on quantitative human health risk assessment as a part of environmental policy making, particularly approaches to cumulative and chemical mixtures risk assessment. Dr. Fox is currently serving on the IOM Committee on Long-term health consequences of exposure to burn pits in Iraq and Afghanistan and served on the NRC Committee on the Health Risks of Phthalates. Dr. Fox received her MPH from the University of Rochester School of Medicine and Dentistry and PhD from the Johns Hopkins Bloomberg School of Public Health. Dr. Fox began her public health career conducting community health studies around hazardous waste sites as a Research Scientist in the New York State Department of Health.

E. Angeles Martínez Mier, DDS, MSD, Ph.D.

Associate Professor

Department of Preventive and Community Dentistry

Indiana University School of Dentistry

E. Angeles Martínez Mier, DDS, MSD, PhD is an Associate Professor (tenured) in the Department of Preventive and Community Dentistry at Indiana University School of Dentistry. She serves as director of the Fluoride Research Program within her department. Dr. Martínez Mier previously held the positions of Preventive Dentistry Department Chair and Coordinator of undergraduate periodontics at the Universidad Intercontinental in Mexico City, Mexico. After receiving her dental degree from the Universidad Nacional Autónoma de México, in Mexico City, Mexico, in 1989, Dr. Martínez Mier completed a Masters of Science in Dentistry, majoring in Preventive Dentistry at Indiana University School of Dentistry, in 1994; and a three-year clinical fellowship in Periodontics, also at the Indiana University School of Dentistry in 1995. She then obtained a PhD in Dental Sciences in 2000 from Indiana University. Dr. Martínez is the past president of the Indiana Chapter of the Hispanic Dental Association and is a member of the International Association of Dental Research, the American Dental Education Association, the American Association of Public Health Dentistry and the European Organization for Caries Research. She has served as consultant for the Division of Oral Health of the Centers for Disease Control and Prevention. She was a member of the CDC Expert Panel on Methods to Analyze Fluoride for the Surveillance of Total Fluoride Intake, and a member and organizer of the CDC Expert Panel on Methods to Detect and Quantify Enamel Fluorosis for Surveillance Purposes. She currently serves as the Chairperson for the American Association of Dental Research Science Information Committee.

Dr. Martínez Mier's research has been funded by grants from the National Institute of Dental and Craniofacial Research, Clarian Health, Delta Dental Insurance, the Borrow Foundation and the West Foundation. Her research projects have received multiple awards. Her research interests are mainly in two areas: fluorides and community health. In the area of fluorides, she is particularly interested in refining analytical methodologies to accurately determine fluoride presence and in the role of fluoride in the onset and progression of demineralization and remineralization. She is also interested in developing methodologies to diagnose dental fluorosis through clinical, photographic and digital imaging evaluations, including dental fluorosis and incipient caries differential diagnosis and in better defining the mechanisms by which fluoride affects the development of dental and skeletal fluorosis, including genetic and environmental factors. Dr. Martínez Mier is engaged in community-based research in designed to address and identify disparities in dental caries and dental fluorosis in Latino/Hispanic patients.

David L. Ozsvath, Ph.D.
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EDUCATION

Ph.D. Geology (1985), The State University of New York - Binghamton
M.S. Geochemistry (1979), The Pennsylvania State University
B.A. Geology (1976), The University of Vermont

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1987 to present Department of Geography/Geology, University of Wisconsin-Stevens Point.
1986 to 1987 Visiting Professor, Department of Geology, Lafayette College, Easton, PA.
1983 to 1986 Geochemist / Hydrogeologist, O'Brien & Gere Engineers, Syracuse, NY.
1981 to 1983 Geologist / Hydrogeologist, Coates & Associates, Inc., Endicott, NY.
1979 to 1983 Teaching and Research Assistant, Department of Geological Sciences,
State University of New York-Binghamton, Binghamton, NY.
1978 to 1979 Geologist, Malcolm Pirnie Inc., Consulting Engineers, White Plains, NY.

RELEVANT PUBLICATIONS

2009 Ozsvath, D.L., *Fluoride and Environmental Health: a Review*; Reviews in Environmental Science and Biotechnology, Vol. 8, No. 1, p. 59-79. (*invited paper*)
2007 Ozsvath, D.L., *Natural Controls on Fluoride Concentrations in a Fractured, Crystalline Bedrock Aquifer*; 30th Annual Applied Geography Conferences, Indianapolis, IN.
2006 Ozsvath, D.L., *Fluoride Concentrations in a Crystalline Bedrock Aquifer, Marathon County, Wisconsin*; Environmental Geology, vol. 50, no. 1, p. 132-138.
2006 Ozsvath, D.L., *Fluoride in a Sole Source, Crystalline Bedrock Aquifer, Marathon County, Wisconsin*; Geological Society of America Annual Meeting, Philadelphia, PA, http://gsa.confex.com/gsa/2006AM/finalprogram/abstract_105521.htm.

Reviewer Post-Meeting Comments

Linda C. Abbott, Ph.D.

1. Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.

The document under review – Fluoride: Exposure and Relative Source Contribution Analysis – should be reorganized to provide an overview of the question it seeks to address and the methodology by which it does so. The impact of the Dean (1942), McClure (1943) and Ershow and Cantor (1989) should be explained early in the document. Providing this overview at the beginning would put the other material in context when it is encountered. As the document is currently organized, you don’t fully realize the importance of these older studies until after you have read about them. The paragraph at the bottom of page 2 onto the top of page 3 is insufficient notice of the significance of the older studies and the manner in which they must be used to reconstruct the exposure in the historical period. The document does not fully explain why the calculation of the relative source contribution (RSC) must rely on historical data rather than using more current exposure data for foods and beverages.

The document would be strengthened by including a “road map” at the beginning describing the usual process for establishing the relative source contribution (RSC) and the adaptations to that process that were required in order to assess fluoride. Including the equation to calculate the RSC in the first section would help set the stage for what follows. A flow chart depicting the types of information usually required and the source of the information for a typical chemical versus fluoride would help the reader appreciate the approach used and the information that follows. As currently organized, it is unclear why there is an encyclopedic description of fluoride in foods from the 40’s and 50’s through the current time until chapter 6.

The first section should also provide an overview of the unique challenges associated with setting the RSC for fluoride. From my initial reading of the document these challenges appear to include: 1) dose-response data used in the proposed RfD are from an era where the proportion of fluoride from food, water, soil and dental products differs from the relative proportion attributed to these sources today; 2) historical data estimating fluoride exposure through food and water may not reflect a nationally representative estimate; 3) historical data do not separate fluoride exposure from food from exposure from drinking water; 4) historical data frequently do not disclose actual food amounts. The historical may not disclose the food items considered, the fluoride concentrations of individual foods and cannot be evaluated to determine whether the historical exposures are representative of the national population; 5) current residue data are lacking in many foods and beverages; 6) fluoridation levels in community water supplies have varied over the historical data period; and 7) there has been an increased use of fluoride in water and dental products during the period of historical data resulting in potentially higher fluoride concentrations in 2010 foods and water than in historical data sets.

The first section should also provide an overview of how the data discussed in the document are to be used in establishing a MCLG or MCL. In section 1.2, the types of data used to estimate the MCLG are discussed. Units for each of the variables should be supplied. The relationship between the MCL and the MCLG should also be discussed here. The equation in section 1.2 does not indicate that the EPA will use body weight data other than that of the 70 kg adult. The MCLG or MCL is expressed in mg/L while the RfD is expressed in mg/kg/d. Some discussion of the relationship between body weight, drinking water intake and the resulting MCLG would help the reader interpret the potential significance of selecting various data sources for age-specific drinking water intake, body weight or

food consumption. It is unclear how the age-specific fluoride exposure estimates in sections 7 and 8 will be used in establishing the MCL or MCLG. An overview of this process in section 1 would be helpful. It is unclear whether in establishing the MCL/MCLG only water consumption from community water supplies is considered. The USDA CSFII and the NHANES survey provide information on the source of the drinking water for each respondent. In the CSFII, there are several possibilities – community water supply, spring water, bottled water, well water or an unknown source. Does the MCL address drinking water intake from only one, several or all of these sources? This should be explained in section 1.

It is assumed that the DWI values reported in Table 6.3 include both direct and indirect community water in the drinking water consumptions (mL/day) and do not reflect other water sources. The EPA reference cited for Table 6.3 (EPA, 2004 – The Estimated Per Capita Water Ingestion and Body Weight in the United States – An Update) estimates that for children less than two years, indirect water consumption is greater than direct water consumption in the consumers only population that consumes community water (Part IV, Table A2, p. E-144). For other age groups, the indirect water consumed relative to the total direct plus indirect is not an insignificant amount. The EPA estimated per capita drinking water document (EPA, 2004) defines indirect water as “water added to foods and beverages during final preparation at home, or by food service establishments such as school cafeterias and restaurants” and defines beverages to include milk, soft drinks, tea, coffee, juices as well as many others listed in Figure 3.4 of EPA, 2004. Beverages include reconstituted juices, instant coffee, coffee and tea brewed at home with water added at home or in a food service environment. The indirect water used to reconstitute these beverages or create them from dry powders is considered in the indirect water consumption reported in EPA, 2004. For example, the community water intake for a subpopulation such as children from 6 months to less than 1 year in age includes the indirect water used to reconstitute infant formula. The community water intake for children in the age range from 1 to 3 years includes indirect water used to prepare tea, lemonade, and powdered drinks. The discussion in section 6.1 of the document under review under the beverages subtitle relies heavily on data from Pang et al (1992), Jackson et al (2002) and Singer et al (1985) to estimate fluoride concentration in beverages. It is not clear from the presentation in the review document that double counting of fluoride from indirect water has not occurred by relying on samples in these studies that may have been reconstituted using tap water or some other water source that was not free from fluoride. In that case, fluoride in the beverage source category that is the result of indirect water addition would add to the fluoride from all sources other than drinking water and underestimate the amount available for drinking water. Conversely, it is also unclear whether powdered beverages which contain fluoride absent any addition of indirect drinking water are adequately considered by the methodology used to derive Table 6.2. Further discussion of this would improve this part of the document.

The document does not provide an estimate for the RSC. After reading the document, you do not know what the estimate of the RSC is or how it might be applied to different age-classes. Many different age-specific estimates are provided in section 7, but it is not clear how or whether these estimates will be combined. It seems unlikely that there will be many different MCL values for the same chemical. It may be that the estimate for the most sensitive population group as identified in the dose-response document might inform this, but it is not possible to determine from the text of this review document. Sections 7 and 8 should be expanded to address this issue.

A table summarizing the information given in sections 2 and 3 would allow the reader to quickly scan the various sources of data. Relating these data to the calculation of the variables in the RSC equation on page 114 would be especially useful. Moving this equation to the beginning of the document - perhaps section 1- would provide the reader with a quick overview to the types of information that will be needed to address the primary question posed by the document. Organizing the subsequent

chapters to begin with a reiteration of the equation - highlighting the data that chapter provides - would provide a framework for discussing the material where the reader can immediately understand the relevance of that chapter to the overall goal.

The use of a variety of different units creates an obstacle which makes easy comparison between tables, the text and figures impossible. If possible, conversion of the values into the same unit would highlight where differences may be found. The relationship between the RfD (expressed in mg/kg/d,) MCL/MCLG (expressed in mL/d,) and fluoride exposure in mg/d is especially important to clarify.

The document presupposes knowledge of the contents of U.S. EPA (2009a). The discussion in section 8 on the Dean and McClure studies and their relevance is particularly difficult to fully understand without this underlying document. Perhaps the final relative source contribution analysis will combine U.S. EPA (2009a) with this document and there is not a great need to repeat information from that document here. But if this is to be a stand-alone document, much further discussion of the contents and rationale used in EPA (2009a) is required. It would be useful for peer reviewers to have copies of some of the critical foundational documents upon which the review document is based. With an abbreviated time period in which to conduct a peer review, too much time was spent located the underlying studies.

The Reference Dose (RfD) is not fully explained at an early point in the document. The OW proposed RfD (first identified on page 120) is 0.08 mg/kg/d. The last paragraph on p. 120 describes the derivation of the proposed RfD from “the 95th percentile lower bound drinking water (1.87 mg/L) associated with a 0.5% prevalence of severe dental fluorosis in the population studied by Dean (1942).” This information should appear much earlier in the document to alert the reader to its significance when first presented with the data from the Dean study. The Dean study is mentioned substantively for the first time on p 71, again on p. 74 before its mention on p. 120. Due to the significance of the Dean study in the estimation of the RfD and the use of the scoring, it should be described much earlier.

2. Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.

The section on uncertainty (§6.5) discusses many important sources of uncertainty but does not attempt to quantify the effect of these sources of uncertainty on the estimates used in the RSC estimation. The document states that in recognition of these uncertainties the values selected for the various sources of fluoride intake were average to slightly above average. It is unclear how the average fluoride intake was determined in order to select values that were average or above average and whether average refers to the average intake value from across the available studies or some other estimate of expected average exposure. Without actually determining the “average” intake, it is unclear how the agency selected studies to ensure that at least the average intake is demonstrated by the representative studies. Given the degree to which the analyses rely on older historical data from studies of populations that may not be representative of the current food and water consumption rates for the U.S. population, more should be done to assess the uncertainty of relying on these studies. A quantitative estimate of uncertainty, at least for some of the individual studies used for food intake, could be conducted and would demonstrate some of the uncertainty associated with the representative studies. The uncertainties resulting from using the residue data without adjusting for bioavailability of fluoride in certain types of foods (bones, seafood) and perhaps from the toothpaste-related fluoride intake could be addressed quantitatively as well.

The uncertainty about the RSC values for each age class (Table 7.1) could be estimated by incorporating the uncertainty about each intake source (e.g., food, drinking water, soil, etc.) into an error analysis if the fluoride exposure for each intake is the average expected value and the distributions are normal. Perhaps a sensitivity analysis for the variables in the RSC equation could inform the agency of which variables most influence the RSC value and then conduct an uncertainty analysis about the estimation of intake for those highly influential variables.

There should also be clarification of whether the use of sulfuryl fluoride is expected to increase, as a relative share of the percent of the crop treated. With the reduction in methyl bromide use and the restrictions on telone and iodomethane in some states and prospects for phosphine as a substitute for methyl bromide, it could be possible that sulfuryl fluoride use may increase. Some discussion of the dynamic nature of the fumigant market might provide additional information to qualitatively discuss uncertainty with respect to future exposure levels due to sulfuryl fluoride.

There are uncertainties about the use of the USDA Continuing Survey of Food Intakes by Individuals (CSFII) two-day water consumption values for the youngest age class considered. The EPA’s Estimated per Capita Water Ingestion and Body Weight in the United States—An Update is based on data collected by the United States Department of Agriculture’s 1994–1996 and 1998 Continuing Survey of Food Intakes by Individuals and does not take into account the age of the respondent at both dates in the CSFII. For many of the younger age classes, an error may be introduced if it is assumed that the individual is in the same age class for both of the sampling dates. This is especially important if the age classes are divided into months, reducing the number of respondents per age class. For example, some of the respondents in the under one month category for the first day of the survey are in the next category (one month old) or even the category after that for the second day. Both survey dates are recorded in the CSFII and some dietary data can clearly be identified as being associated with the next survey age class through subtraction of the early date (day 1) from the later date (day 2). For example, seven respondents consuming community water in the less than one month age category have more than 30 days (more than 1 month) between day 1 and day 2 survey dates. It can be assumed that day 2 for these respondents does not represent the water consumption rate of an under one month old. These seven drinking water consumptions are among the highest for that age class. While for fluoride the youngest age class spans 6 months and probably contains more respondent records than the less than one month category described above, there is still the chance that some of the records included actually are records of respondents who are over one year in age. The drinking water estimate for this youngest age class could be overestimated if those inappropriately combined respondents consume more drinking water per day than those who belong in this category. For at least this youngest age class, the total, direct and indirect drinking water consumption estimates should be examined to determine whether inappropriately combined respondents might be biasing the estimate.

The DWI (Table 7-1), based on the 90th percentile intake with average 0.87 mg F/L, reflects consumers only. This intake level, while conservative, may overestimate exposure. The 90th percentile consumption for the entire population and the mean consumption level should also be examined in the RSC equation. Comparing the three calculated sets of RSC values will provide some information on how much error may be incorporated by using a consumers-only 90th percentile consumption to estimate drinking water exposure with the average general population exposure for the other components of the RSC equation.

- 3. Please consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may for alternative studies that you believe are more representative of exposures.**

In general, there is inadequate information about the studies (for food) underlying the exposure estimates to evaluate their adequacy. There is little or no discussion of the consumption rates for foods (mg food per day or per body weight). Without further data, it is difficult to determine the representativeness of a study that involves only a few individuals or one sex (Singer et al., 1980; San Filippo and Battistone (1971)) or few geographic areas (Pang et al, 1992; Jackson 2002; Singer et al, 1980; San Filippo and Battistone (1971)) to use it as a proxy for the national population even for a specific national subpopulation.

It is not clear why representative exposure data from past studies is used. An explanation of why it is not possible to estimate the current fluoride exposure from food should be clearly stated. It may be that the agency finds the current database of fluoride concentrations in food inadequate to estimate fluoride intake through food for the U.S. population. Such an explanation is necessary because the most of the studies selected to represent fluoride intake through food for the various age categories required by the agency are not representative of the U.S. population, provide little information on actual food intakes of the subjects and appear to conflate fluoride concentration in foods with food intake rates by reporting only the fluoride exposure estimates (mg fluoride/day) for the small populations they study.

As an alternative approach, it may be possible to construct a method of extrapolating from the foods for which fluoride concentration data exist (USDA, 2009) to the U.S. population and various subpopulations of interest using the CSFII average consumption rates for various foods or food groups. The FDA Total Diet Study uses a similar approach to extrapolate from the 260+ foods analyzed in the Total Diet Study (TDS) market baskets to the U.S. population. Using a similar approach here would require comparing the existing data base for which fluoride concentrations in foods exist and making some decisions about which other CSFII foods could be represented by the foods that have been analyzed. This approach has advantages to relying on historical data to estimate fluoride exposure through food. First, the consumption rates used are nationally representative of recent trends in consumption. (A similar approach could be done using the most recent NHANES dietary survey, but to my knowledge there is not already a 1:1 mapping between the various foods in the survey as there is for the CSFII through the TDS tools.) Second, the most recent fluoride concentrations in food items could be used. Third, this approach would not conflate the historical fluoride concentrations in food (and possibly indirect water) with unknowable consumption rates to arrive at an exposure estimate that may be more reflective of a unique subpopulation at an earlier time in history than today’s population. Fourth, because the underlying data (consumption rates and fluoride concentrations in food) are transparent and available, a more sophisticated uncertainty analysis for the food exposure for each age class could be conducted.

The Food Commodity Intake Database provides recipe translations which could be used to estimate both indirect water consumption and direct water consumption by the U.S. population. If the current measurements on fluoride in food could be mapped to those foods not measured as done in the TDS survey, it may be possible to estimate exposure given current consumption patterns. The EPA Office of Research and Development (ORD) is presenting their Stochastic Human Exposure Dose Simulation model (SHEDS) dietary model before the FIFRA Scientific Advisory Panel this July.

This model will allow the use of residues in foods (like TDS residues in foods) as well as estimation of residues in foods from residues in raw agricultural commodities in the same model run. Perhaps the Office of Water could collaborate with ORD to use this new model to estimate the dietary (food and beverage) and water exposure to fluoride.

4. Please comment on EPA’s rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically justified and clearly and objectively described? What changes or improvements would you suggest?

First, the selection of the age groups needs further discussion. It is unclear why the specific age groups need to be assessed. Section 2.5.5 states these age classes are equivalent to those used in the dose-response document (EPA, 2009a) but it is not until the next page that the document discusses the need to organize the data into age classes equivalent to those from Ershow and Cantor (1989) because [Ershow and Cantor?] report drinking water intake data for the period closest to that of the Dean study (1942). Even in section 2.5.5, the significance of the drinking water intake in Dean (1942) is not explained. It is not until page 120 in section 8.2 that the significance of the Ershow and Cantor study begins to be addressed. This needs to be explained much earlier in the document to prevent the reader from asking some of the questions below which reflected my understanding the first several times I read this section. Why do the age ranges differ from those used in the dietary assessment from OPP for sulfuryl fluoride? Why are these particular ages of special interest? Is the rationale for the various age groups due to differences in consumption or special sensitivity to the effects of fluoride? This needs to be discussed in more depth. Some explanation is needed for the differing presentation of the label for each age class. Four of the classes are bounded on the high end by a < X form, while the other two age classes appear to be bounded by a particular age (e.g., 1-3). The same presentation and analysis should be used for each unless there is a disclosed reason for the difference.

The average food exposure for infants is probably too high. (See discussion below on food intakes)

The average drinking water exposure for infants may be too high (see earlier discussion on uncertainty about drinking water consumption values.)

The discussion of the contribution of sulfuryl fluoride to dietary exposure from food is difficult to follow and complicated by the use of age ranges not used in the OPP assessment. There should be clarification of whether the OPP estimates are based on tolerance level exposure or not. (See discussion of sulfuryl fluoride below)

Combining average exposures for individual sources should not also include an upper level percentile exposure value for one of the sources. Using the equation on page 114 to calculate the RSC assumes that the denominator represents the total exposure to fluoride from all oral sources. Adding the mean exposures from each of these sources will produce an estimate of the mean total exposure. Adding the mean exposures from all but drinking water and then adding the 90th percentile drinking water exposure will not produce an unbiased estimate of total exposure.

5. Please comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication, as supported by the concentrations found in various food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940’s?

This issue is especially difficult to evaluate without the dose-response analysis for fluoride (EPA, 2009a) or the Dean (1942), Ershow and Cantor (1989) and Maguire (1943) studies. It appears that this issue relates to dose construction from various sources of fluoride exposure underlying the dental

fluorosis response in the Dean study. This needs to be discussed at the very outset of the document. The first few times I considered this question it was unclear why it was necessary to estimate the fluoride concentration from the 1940's. Without further explanation of the dose-response analysis, it is not clear why the fluoride concentration in drinking water from the 1940's is not a dead letter. More background on the need for such an approach is necessary.

Section 2.5.5 states the age classes used are equivalent to those used in the dose-response document (EPA, 2009a) and goes on to assert that Ershow and Cantor (1989) report drinking water intake data for the period closest to that of the Dean study (1942). The discussion of these drinking water intakes in section 8 is complex and really requires the underlying dose-response analysis (EPA, 2009a) to fully appreciate. Given that the dose-response analysis was not provided to the peer review committee, it is difficult to follow what is probably one of the most significant chapters in the document under review. While question 5 does not ask the peer review committee to opine on the use of the Ershow and Cantor study, it appears to be fundamental to addressing the adequacy of the McClure data for estimating the fluoride intake from food in the 1940's.

This question appears to flow from the discussion on page 122 to 123 in chapter 8.

The McClure (1943) data appear to overestimate the fluoride concentrations reported in the USDA 2005 data as shown in Table 2-25 in some cases. The USDA 2005 data appear to combine data from multiple sources and are not constrained to estimation of food intakes in the 1940's. It is not clear why comparison of concentration values in McClure to those in USDA 2005 provides confidence that McClure is representative of the intake through food in the 1940's as stated on page 122. McClure (Table 2-59) apparently only analyzed 10 different foods – milk, cheese, chicken, frankfurter, white bread, apples, fish, spinach, tomatoes and carrots. This only describes fluoride concentration and not consumption rates.

The issue of fluoride intake (mg/d) is addressed on page 53 in the market basket studies section. No estimate of the consumption rate of the foods by various age groups is given – only the final product of fluoride intake given various assumptions about the concentration in water and food. The discussion of McClure's assessment of fluoride in dry foods is particularly intriguing as none of the 10 foods listed in Table 2-59 is described as dry or based on dry weight in McClure 1943. It is unclear, without reading McClure, how “dry” is used in the analysis. Basing the exposure from food on only ten food items without any explanation of how (or whether) these ten foods are extrapolated to the rest of the diet would appear to incorporate a large amount of uncertainty about the estimate of exposure through food. If these are the only available data to address the question the agency poses – what is the contribution of food to the total fluoride exposure in 1942 – some type of quantitative uncertainty analysis should be performed.

There are additional reservations in combining the age groups and body weights reported by Dean (1942) with different (?) age groups and body weights (?) reported in McClure. The discussion on page 122 of the McClure data assuming foods with 0.5 ppm fluoride should refer to Table 2-41 as the data reported in Table 8-3 appear to rely on these data. One suspects this section of the report (§8.2) contains the key findings of the document under review, yet this section does not describe in adequate detail why the 1942 McClure data are important. These data do not appear to be used in this section except to adjust the RfD by 0.01 mg/kg/d for the contribution of solid food. This issue – the derivation of the RfD – would appear to be better addressed in the previous document on dose-response analysis (EPA, 2009a).

Although not relevant to the question posed to the peer review committee, the rest of §8.2 does not describe well how the figures were derived. The relative contribution of each of the sources to total

fluoride exposure is shown in Fig. 8.1 but no clear explanation of how these values were calculated is given. The other figures are equally puzzling with respect to the source of data.

- 6. Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.**

Consider adding these citations (for completeness more than specific information – they may not actually be helpful. Time did not permit reading all of these):

[Rao GS](#), 1984. **Dietary intake and bioavailability of fluoride.** [Annu Rev Nutr.](#) 1984;4:115-36.

Yakav et al. 2007. Determination of exposure and probable ingestion of fluoride through tea, toothpaste, tobacco and pan masala. *Journal of Hazardous Materials* 142 (2007) 77–80.

[Zohouri FV](#), [Maguire A](#), 2006. Sources of dietary fluoride intake in 6-7-year-old English children receiving optimally, sub-optimally, and non-fluoridated water. [J Public Health Dent.](#) Fall;66(4):227-34.

- 7. Please provide any additional comments and/or further suggestions you may have for improving the document.**

Several comments do not fit neatly in the context of the charge to the panel. First, the question on the adequacy of the studies selected and the representativeness of the values selected (Q. #3) and the question on EPA’s rationale for selecting certain data items (Q.#4) are related and rather than repeating the answers for each of them, a combined answer appears below. Second, some issues on the fumigant sulfuryl fluoride arise in the document. These are discussed in turn below. Finally some page by page comments are provided.

Food intake

The representative food intake in Table 7-1 is based upon data from Table 6.1 which is in turn based on several tables from section 2. The data from Table 6.1 need further support. First, it is unclear whether the underlying studies cited in the rationale use the same age groups as Table 6.1. If not, further explanation is needed to describe how the data from the original papers were categorized using the age groups in Table 6-1. The use of the term “intake” in the second paragraph in §6.1 is confusing. The term “intake” appears to be used differently in the phrase, “intakes for non-beverage food groups come from USDA” than the title for Table 6-1, “Estimated Daily Dietary Fluoride intakes.” In the first phrase it is assumed “intake” means consumption rate of a particular food or food group, while in the second case “intake” appears to mean “exposure estimate” of fluorine mass per day. The definition or use of the term “intake” should be clarified when it is used.

Age 0.5 to < 1 year – The market basket study by Ophaug (1985) does not appear to contain the data in Table 2-58 cited as a reference in Table 6-1. Table 2-58 reports results from a study of adult hospital diets. Data from the Ophaug (1985) study are found in Table 2-34. There is insufficient data in the description of this study to evaluate whether the data form an adequate basis for the F intake in the youngest age class. While the study examined 44 market baskets in 20 cities, it is unclear how many actual foods were included in those market baskets and how representative they may have been of the diet

for this age class. Reporting only the F intake in Table 2-34 does not indicate the consumption assumed for the foods analyzed in the market baskets. Fourteen-day consumption records are rare – there is no discussion of how the “average” fourteen-day consumption record was created. Dietary intake of a possible contaminate through food is a function of both the concentration of the contaminant in the food item and the amount consumed. Different types of uncertainty are associated with each of these components of the equation. Here, in Table 2-34, the summary estimate of F intake is the product of both consumption and concentration, but there is no way to evaluate the adequacy of either estimate. It is unclear how representative the “average” fourteen day consumption may be for either 1985 or 2010.

Table 2-34 shows the daily fluoride exposure (mg/day) from food and total dietary. Back calculating the body weight (kg) and water consumption (mL/day) results in a different body weight value and water consumption value for each of the 22 market basket/year combinations. This implies that each market basket/city combination involved a unique elicitation of the consumption values and that drinking water consumption differs between the cities.

Table 6-1 states the overall mean from Ophaug (1985) (0.17 mg/d) was adjusted by subtracting the milk/formula intake from the earlier Ophaug study and then adding the 0.14 mg/d estimate from the powdered formula study by Van Winkle et al., 1995 using tap water to make the formula. This almost doubles the original Ophaug estimate and appears to be an incorrect combination of a fluoride concentration in food (Van Winkle et al. 1995) with an exposure estimate (Ophaug, 1985). To add the Van Winkle study to the Ophaug study, you would have to know how much formula was consumed in the Ophaug study. If the results from Van Winkle really are concentrations and are reported in mg/L (and not in mg/kg or some mass-mass basis) you would have to know the amount of liters of formula consumed in Ophaug to estimate the mg F/d contributed to the diet.

The document under review is particularly unclear about what these data from Van Winkle might represent. On page 44, the Van Winkle data are reported to be the mean concentration of fluoride in powdered concentrate infant formula (0.14 mg/L). Van Winkle et al. performed their analysis of the powdered concentrate using distilled water. Later in Table 2-60, the 0.14 mg/L Van Winkle value is presented as an “exposure estimate” in units of mg/day. This could only be correct if the average consumption of powdered concentrate by infants in this age range is 1 L/d. There is no discussion of this calculation and the data in the table column labeled “mg/d” is noted parenthetically for Van Winkle as (mg/L). This appears to be a mistake, but without reading the original source whether it is a mistake or not cannot be determined. The note in table 2-60 associated with the Van Winkle data raises another issue. The note states that fluoride intakes will be based on formula intakes assuming the formula is prepared with tap water at the average fluoride concentration (0.87 mg/L). This suggests that indirect water – the amount of water used to reconstitute the formula – is added into the infant drinking water estimate somehow. This is not well explained. Table 6.3 states that the 90th percentile intake of drinking water (USEPA, 2004) is used to estimate fluoride exposure assuming the 0.87 mg/L F concentration. The drinking water consumption data for this age group is not matched with consumption data used by Ophaug in the 1985 study of 22 market baskets. First, the 90th percentile of drinking water consumption is used but the average exposure from food is used. The food exposure value contains no information about its relation to the distribution of drinking water consumption. It may be that the average food consumption (and hence exposure as reported here) is not related to the 90th percentile water intake. There is not enough information about the Ophaug study to evaluate the adequacy of this approach but it seems optimistic that combining these two disparate data sources for fluoride exposure through food (Ophaug) and exposure through water (EPA 2004) does not result in some under or over estimation for the combined food and water exposure by this age class.

Age 1 to < 4 year

The Ophaug study is not well described enough to evaluate whether the consumption data are representative. If the same methodology was used as for the infants – construction of a representative fourteen day diet – the same reservations apply to this study as to the one for the six month olds. Using this study for the food intake value from 2010 foods may not be reflective of today’s fluoride exposure from food. If the concentration of fluoride has increased in foods, this mean estimate from this study may underestimate actual exposure. But there is little data provided on the composition of the two year old diets used here. The EPA review document does not describe in enough detail the methodology used in this study.

Age 4 to < 7

The Jackson study only addresses two localities – Richmond and Connersville, Indiana. These may not be representative of national consumption estimates. The survey was apparently based on a Food Frequency Questionnaire which would provide an estimate of the frequency of consumption but not the amount consumed. The weighting of the 441 items sampled based on the food frequencies is not described in enough detail to understand what was done. It unclear how the weighting factors may have influenced how the 441 items sampled were used to create a composite USDA food groups. It is also unclear what time period the exposure estimate was to represent (1 month? 1 year?). One description of this study (pg 58) states that the 1998 CSFII upper intake data were not available at the time of the study and that the authors estimated upper level intake using the 90th percentile of the fluoride concentration of the food group samples. This would appear to be mixing an upper bound on consumption with an upper bound on contaminant concentration. If this study is to be used by the Office of Water, the correct upper bound consumption estimate should be used to estimate exposure.

Age 7 – <11 and 11 - 14

Relying on the Jackson study for the 7 - <11 and 11 – 14 age groups, in combination with the appropriate USDA food group-level consumption rates, assumes that Jackson adequately sampled foods representative of the U.S. diet for those groups. This is probably not the case. The same issues described above for Jackson are incorporated by reference here.

Adults

The hospital study by Taves is not likely to be representative of adult food intakes. A six-day survey of hospital diets in New York is a sample of a special sub-population (hospitalized adults). Only the fluoride intake (mg/d) from this study is reported in the document under review – it is not possible to determine whether the amount presumed consumed by the patients is similar to consumption patterns in the current non-hospitalized U.S. population. If the consumption rates are given, comparison between these rates and those from a nationally representative survey would give an estimate of the uncertainty associated with using these data as a proxy for the current U.S. population.

The Singer (1980) study is likely not representative of current dietary intake patterns as it apparently relies on food intake reported in 1968 and 1972 consumption surveys. The U.S. diet has changed significantly since that period. If this study is to be used, some attempt should be made to quantify the difference in food intake rates between this survey and the present day. Some estimate of the uncertainty associated with using these fluoride exposures (mg F/d) could be made. It is unclear from the presentation whether the difference in F intake reported in Table 2-52 is due to differences in fluoride concentrations of the foods in the market baskets or also due to differences in consumption rates.

The Singer studies are described as using FDA market basket surveys of 117 food items (Singer 1980, 1985). The market baskets were collected between 1975 and 1982. The FDA provides a mapping between the foods sampled in their Total Diet Study (TDS) and the various foods reported in the CSFII survey. Perhaps these data, if they include fluoride concentrations for foods in the CSFII or its predecessors could form the basis of a dietary assessment using the current consumption rates for these groups rather using the Singer data. It is assumed the market baskets actually measured fluoride concentration in the 117 food items, although not disclosed in the document under review.

Beverage intake (non-water) average

Age 0.5 to < 1 year – Assuming this group ingests no beverages is incorrect. Juices make up an important source of beverages for this group and not all of these juices are reconstituted. It is unclear how powdered or frozen concentrate juices are considered by this analysis. Are they beverages or foods? How is the indirect water used to reconstitute them accounted for in the analysis? A flow chart (see Q#1) would greatly aid understanding here.

The treatment of beverages for the other age classes is confusing. Milk is excluded. Is milk included in the food estimates in the previous section? The separation of beverages from foods is confusing. The use of indirect water in reconstituting powdered or concentrated beverages would appear to be an important exposure pathway for fluoride, yet it is not clear how this pathway is considered in the analysis. The Food Commodity Intake Database recipes explicitly calculate the indirect water used to prepare foods. Not only beverages are reconstituted with “indirect” water – soups and sauces and dehydrated foods are also reconstituted with indirect water. It is unclear why the beverage category is separate from food. It is unlikely that the Pang, Jackson or Singer studies provide a nationally representative estimate of beverage consumption and fluoride concentration of those beverages to serve as reliable estimates in Table 6.2.

Drinking water intake

Age 0.5 to < 1 year – See comments under uncertainty (Q.#2).

Toothpaste intake average

Time does not permit analysis of this

Soil intake average

Time does not permit analysis of this

Sulfuryl Fluoride Issues:

The Reference Dose (RfD) of 0.114 mg/kg/d included in the DEEM output (attachments 1, 2 & 3 of Appendix 1) is never discussed in the document. The 2006 “Human Health Risk Assessment for Sulfuryl Fluoride and Fluoride Anion Addressing the Section 3 Registration of Sulfuryl Fluoride as a Fumigant for Foods and Food Processing Facilities PP# 3F6573” provides some insight into this value as it states that the toxicological assessment for fluoride by the Office of Water used the value of 8 mg/day ([FR 51 (63)]). The 2006 OPP assessment goes on to state the 0.144 mg/kg/d value corresponds to an 8 mg/day intake value (if consumed by a 70 kg adult). The May 28, 2009 EPA OPP Sulfuryl Fluoride - Human Health Assessment Scoping Document in Support of Registration Review (EPA-HQ-OPP-2009-0136-0006) for sulfuryl fluoride lists a chronic RfD of 0.008 mg fluoride/kg bw/d and presents a dietary exposure assessment that differs from the one presented in attachments 2 & 3 of the document under review. While the scoping document (EPA-HQ-OPP-2009-0136-0006) acknowledges there may be a change in the RfD if the EPA OW moves away from using skeletal fluorosis as the toxicological concern, some explanation is needed for the differences between the 2009 OPP scoping document, the two OPP attachments from Appendix 1 and the discussion of the proposed RfD of 0.08 mg/kg/d on page 120.

Beyond the differing RfDs used in the chronic dietary assessment (0.114 v 0.08 mg/kg bw/d) the differences between the estimated exposure levels for the general population and various subpopulations is also needed. In section E of the scoping document, the chronic dietary exposure to fluoride differs from Table 6 (p.11) of appendix 1. One explanation may be the apparent use of the 1989 -1992 CSFII data in the scoping document. While consistency with the OPP dietary assessments may not be crucial, some explanation will be required for any differences between the OW and other dietary assessments performed by the EPA.

It is not possible to determine how the daily intakes of fluoride (mg F/d) were calculated in Table 2.61. The body weights assumed for the age ranges are not given. The body weights appear to come from the list given on page 123 attributed to U.S. EPA, 2004. More discussion (on page 73) is needed as neither the body weight adjustment nor the combination of the original OPP age ranges into new ranges is explained. Using the body weights from page 73 does appear to result in the mg per day intakes reported for the structural or commodity fumigation as the exposures given for the U.S. population from attachments 5 and 6 of Appendix 1.

While it is possible to replicate the mg F/d for the general population using the 70 kg body weight to express the DEEM estimate expressed in mg/kg/d as mg/d, it is not possible to replicate the exposure in terms of the new age categories required by the Office of Water. It is unclear how the DEEM output was combined into the new age ranges. It is not clear why these particular age ranges are required by the Office of Water. The explanation -that the projections were matched as in section 2.5.5. - is not helpful as it was equally unclear what was done in that section. It is unclear why the Office of Water matched the age group projections from DEEM to the Office of Water defined age groups - DEEM could explicitly produce the values that the Office of Water requires by defining custom populations could be created to generate the chronic exposure for 1 to 3 year olds, 4 to 6 year olds or any other age-sex combination required. That would seem to be the easiest way to obtain data in the age class format required by the Office of Water and would also seem to introduce less error than combining the original age classes in the DEEM output in the appendix.

Adding the fluoride exposure associated with structural and food fumigations (as in Table 2.61) assumes both of these exposures are simultaneously occurring for the same individuals. It is entirely possible that someone would be exposed to fluoride residues from food fumigation and not to residues from structural fumigation or vice versa. Where only 0.4% of the crop is treated, it seems unlikely that a person would consume both the structurally treated and the commodity fumigated form of a commodity. As long as only the **mean** values are being added, the resulting total mean exposure would be acceptable, but if some other value in the distribution is used (upper percentile exposure) it would be incorrect to add these together. DEEM could be used to assess the aggregate exposure to both sources of fluoride residues, but adding the two separate exposures is probably not correct.

From the Flutriafol **REVISED** Human-Health Risk Assessment for Proposed Uses on Apple and Soybean (EPA-HQ-OPP-2009-0184-0010)- **“HED has previously conducted separate dietary exposure analyses for fluoride residues from the insecticides cryolite and sulfuryl fluoride as well as from naturally occurring fluoride residues in food and water.”** A summary of the HED analysis would be helpful as the flutriafol analysis suggests that HED has assessed naturally occurring fluoride in food and water. If this is true, perhaps the Office of Water could use the HED analysis for some of the representative values needed in Tables 6-1, 6-2, 6-3. “It was noted that many pesticides contain the fluorine atom, but it was assumed that only cryolite and sulfuryl fluoride would result in meaningful increases in fluoride residues as compared to background levels (presumably due to the lack of carbon-fluorine bonds in these two compounds).” It appears as though HED has conducted an analysis of background levels of fluoride in foods and water. This analysis may have useful

information for OW – it would be useful for the reader to understand what HED did in its dietary exposure analysis. Table 5.1.8.2. is a summary of the fluoride residue estimate in soybean from flutriafol and the fluoride residue estimates incorporated into the sulfuryl fluoride and background dietary exposure analyses (cryolite not registered for use on soybean). Based on this comparison, flutriafol is not a significant contributor to fluoride residues in soybean.

Page by page comments:

p. 12- Many of the studies relied upon by this document involve human experiments. For example, the Trautner and Siebert (1986) study exposed healthy adult volunteers to oral doses of fluoride. Has the use of these data been evaluated by the Human Studies Review Board or some equivalent body?

p. 18 – Table 2-6 gives the fluoride concentration of fruit juices in mg/L while the concentration of other foods are given in mg/kg. Could these data be converted to mg/kg using the specific gravity of the juice to allow comparison between the different foods in the table?

p. 19 – Table 2-7 reports fluoride concentrations in mg/L for foods that normally would not be considered to be liquids – strained meats and strained vegetables. Some explanation is necessary for use of this unit. Is it used in the original reference?

p. 22 – The McClure (1949) study is described as reporting fluoride content on wet and dry weight. It is unclear whether these foods were analyzed as prepared or not. If dry weights are given, can these be used to explain the dry weights reported in Table 2-41 lines e through h attributed to McClure (1943). It is unclear where the dry weights in McClure (1943) are derived.

p. 49 - Table 2-35 should use the same nomenclature for standard error as used in the preceding text. The SEM abbreviation in the table is assumed to standard error of the mean – this should be defined as does the SE used on the preceding page in the text. The choice of the three categories in Table 2-35 is unclear. Were these selected by the author or reanalyzed by OW? Why are they included?

p. 63 – Table 2-50 is entitled “Fluoride Intake from foods.” The table shows both fluoride intake in food and the concentration of fluoride in drinking water. Due to the limited data on study methodology (no information on food preparation techniques, unclear whether estimates include indirect water containing fluoride level in drinking water, etc.) this study is of limited use.

p. 86 - Define the term SMCL in the text. This may be the first time it appears in the text. Although it is in the definitions on page 10, it should be defined here.

p.115 - Table 7-1. Are the representative values based on average consumption and F concentrations?

Mary A. Fox, Ph.D.

1. Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.

To improve overall clarity and transparency the document needs a statement of purpose or problem statement that articulates the questions to be answered. This section should lay out the approach that will achieve the stated purpose. The approach will describe the data and analyses in each chapter and how each chapter fits together to answer the questions. A figure or flow chart depicting the approach would also be helpful. The figure should also reflect the connections to other documents in the Fluoride risk assessment, particularly the dose-response document.

Chapter 8: The public health implications of the exposure assessment become clear in Chapter 8. It is critical that the analyses and information are presented as clearly as possible. The analyses presented in section 8.2 (from last paragraph of page 120 to Table 8-4 on page 123 and particularly the interpretation of Table 8-2 in the last paragraph of page 121) are very hard to follow. The statement of purpose and a chapter-specific approach (as described above) will help. (Further comments on Ch 8 in response to #7).

2. Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.

The uncertainty discussion (section 6.5) should include the direction of uncertainty related to the key data used. Does the available data overestimate, underestimate or both? Can the sources of uncertainty be prioritized? Are the different analytical methods contributing to more uncertainty than changes in diet? How does an understanding of the largest sources of uncertainty help us understand the data or help us characterize the analyses?

Trend of increasing F exposure can be mentioned again in section 6.5.

3. Please consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may for alternative studies that you believe are more representative of exposures.

I would like more information on the quality of the various exposure assessment methodologies (Section 2.5.1) – are any of these methodologies preferable for the purpose of exposure characterization or were they all seen as equally valuable?

I am not aware of other studies to add.

4. Please comment on EPA’s rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically justified and clearly and objectively described? What changes or improvements would you suggest?

I would like to see text on the criteria used to identify the key data/studies. What were the important considerations for being “representative”? Following on response to #3, were studies using a particular methodology preferred ?

- 5. Please comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication, as supported by the concentrations found in various food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940’s?**

I think the approach is reasonable but the need to estimate F from food intake for the 1940’s is not clearly explained (this belongs up front in the purpose/problem statement as described in response to #1).

The selection of 0.5 ppm from McClure (1943) as the estimate for F in solid foods is also not clearly explained or supported in the document. The analysis of the McClure data must be very carefully and completely spelled out and documented. The relationship between McClure’s estimates and more recent data is presented (Table 2-25) and possible explanations for differences are offered. More important is how does the more recent data affect the analysis of the McClure data and the selection of 0.5 ppm as representative of F in solid food in the 1940’s?

- 6. Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.**

I do not have any suggestions for additional references.

- 7. Please provide any additional comments and/or further suggestions you may have for improving the document.**

Pg 79: Can get an estimate of percentage of kids under age 14 from US census

Pg 85, top: Is there a more recent reference (or personal communication) for statement about CDC’s temperature dependent F concentration recommendations. Reference cited is from 1995.

Page 121: Term “margin of exposure” is used incorrectly here. Margin of exposure is not the best way to describe the estimated dose differences at issue. This section (bottom of page 121 to middle of 122) is very confusing. What is the meaning and implication of “OW felt that a 0.01 mg/kg/day difference between the IOM adequate intake estimate and a dose from drinking water that could cause severe dental fluorosis was too small”? Why is a difference of 0.02 mg/kg/day “reasonable” but 0.01 mg/kg/day difference too small? More explanation/justification is needed here.

Page 125: Interpretation of exposures over RfD – such exposures are of concern for increased risk but it is not quantifiable risk information – increased risk is not proportionate to dose or exposure increases. See definitions of hazard index and hazard quotient (attached as last page).

Typos:

Page 54, Table 2-41 last row 4-6 years column – extra decimal point/decimal point placement

Page 96, Table 4-7, col 5 last row, replace “/” with decimal point

Page 101, 2nd line, misplaced parenthesis should read “as reported by U.S. EPA (1988)”

Page 103, Table 5-2, missing parenthesis, column 2, 32 month column

NATA glossary HQ/HI:

Hazard index (HI):

The sum of hazard quotients for substances that affect the same target organ or organ system. Because different pollutants may cause similar adverse health effects, it is often appropriate to combine hazard quotients associated with different substances. EPA has drafted revisions to the national guidelines on mixtures that support combining the effects of different substances in specific and limited ways. Ideally, hazard quotients should be combined for pollutants that cause adverse effects by the same toxic mechanism. However, because detailed information on toxic mechanisms was not available for most of the substances in this assessment, EPA aggregated only the effects of different respiratory irritants. The HI for respiratory irritation is only an approximation of the aggregate effect on the respiratory system (i.e., lungs and air passages) because it is possible that some of the substances cause irritation by different (i.e., non-additive) mechanisms. As with the hazard quotient, aggregate exposures below a HI of 1.0 will likely not result in adverse noncancer health effects over a lifetime of exposure. However, an HI greater than 1.0 does not necessarily suggest a likelihood of adverse effects. **Furthermore, the HI cannot be translated to a probability that adverse effects will occur, and is not likely to be proportional to risk.** A respiratory HI greater than 1.0 can be best described as indicating that a potential may exist for adverse irritation to the respiratory system.

Hazard Quotient:

The ratio of the potential exposure to the substance and the level at which no adverse effects are expected. If the Hazard Quotient is calculated to be less than 1, then no adverse health effects are expected as a result of exposure. If the Hazard Quotient is greater than 1, then adverse health effects are possible. The Hazard Quotient cannot be translated to a probability that adverse health effects will occur, and is unlikely to be proportional to risk. It is especially important to note that a Hazard Quotient exceeding 1 does not necessarily mean that adverse effects will occur.

<http://www.epa.gov/ttn/atw/nata/gloss.html>

E. Angeles Martínez Mier, DDS, MSD, Ph.D.

1. Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.

Page 2, third paragraph, section 1. Introduction, subsection 1.1. Background, states that “...based on data relating fluoride concentrations in drinking water to the prevalence of severe dental fluorosis in selected towns distributed across the United States (Dean, 1942). A clear rationale should be provided for the choice of data. Although this information can be inferred later in the manuscript, mentioning it in this section would improve clarity.

In page 2, fourth paragraph, section 1. Introduction, subsection 1.1. Background, fluoride gels and foams should be added to dental products.

In page 6, first paragraph, section 2. Exposure from Foods and Beverages, mass spectrometry, gas chromatography, electro-analysis, catalytic- enzymatic and radio-analytical methods should be added when describing the newer methods employed for fluoride analysis.

In page 6, second paragraph, section 2. Exposure from Foods and Beverages, Subsection 2.1. Analytical Methods, the different approaches currently employed to determine fluoride could be better described. These may require more than the three distinct phases described and include pretreatment of samples, separation and concentration of fluoride, actual measurement of fluoride ions, calculations of final concentrations per unit of sample, and presentation of the data. Differences have been reported in all of these steps.

In page 6, third paragraph, section 2. Exposure from Foods and Beverages, Subsection 2.1.1. Sample preparation only describes preparation for solid foods, but later in the manuscript, beverages are included as foods. This section should describe sample preparation for both solid foods and beverages.

In page 6, third paragraph, section 2. Exposure from Foods and Beverages, Subsection 2.1.1. Sample preparation should mention that a trapping medium is required to ensure fluoride is not lost during both diffusion and digestion processes.

Page 6, fourth paragraph, section 2. Exposure from Foods and Beverages, Subsection 2.1.1. Sample preparation states that “..ashing of the food samples is used to remove the organic matrix.” I suggest the sentence is changed to say “has been used”, since ashing of the samples is no longer a common practice. A review of the literature shows that all food fluoride American studies described in the manuscript and most international studies since 1990 (see attached table 1.– articles hyperlinked to Pub Med), use a modification of the micro diffusion method of Taves (cited in the manuscript) with a pretreatment of homogenization using a commercially available blender.

[Fluoride content of powdered infant formula meets Australian Food Safety Standards.](#)

Clifford H, Olszowy H, Young M, Hegarty J, Cross M.

Aust N Z J Public Health. 2009 Dec;33(6):573-6.

[Fluoride intake from meals served in daycare centres in municipalities with different fluoride concentrations in the water supply.](#)

Pagliari Tiano AV, Moimaz SA, Saliba O, Saliba NA, Sumida DH.

Oral Health Prev Dent. 2009;7(3):289-95.

[Fluoride ingestion from food items and dentifrice in 2-6-year-old Brazilian children living in a fluoridated area using a semiquantitative food frequency questionnaire.](#)

Miziara AP, Philippi ST, Levy FM, Buzalaf MA.

Community Dent Oral Epidemiol. 2009 Aug;37(4):305-15. Epub 2009 Jun 9.

4. [Dietary fluoride intake by children receiving different sources of systemic fluoride.](#)

Rodrigues MH, Leite AL, Arana A, Villena RS, Forte FD, Sampaio FC, Buzalaf MA.

J Dent Res. 2009 Feb;88(2):142-5.

[Fluoride intake and urinary excretion in 6- to 7-year-old children living in optimally, sub-optimally and non-fluoridated areas.](#)

Maguire A, Zohouri FV, Hindmarch PN, Hatts J, Moynihan PJ.

Community Dent Oral Epidemiol. 2007 Dec;35(6):479-88.

[\[Fluoride concentrations in typical Brazilian foods and in infant foods\]](#)

Casarin RC, Fernandes DR, Lima-Arsati YB, Cury JA.

Rev Saude Publica. 2007 Aug;41(4):549-56. Portuguese.

[Fluoride ingestion from toothpaste and diet in 1- to 3-year-old Brazilian children.](#)

de Almeida BS, da Silva Cardoso VE, Buzalaf MA.

Community Dent Oral Epidemiol. 2007 Feb;35(1):53-63.

[Sources of dietary fluoride intake in 6-7-year-old English children receiving optimally, sub-optimally, and non-fluoridated water.](#)

Zohouri FV, Maguire A, Moynihan PJ.

J Public Health Dent. 2006 Fall;66(4):227-34.

[Fluoride intake from food and liquid in Japanese children living in two areas with different fluoride concentrations in the water supply.](#)

Nohno K, Sakuma S, Koga H, Nishimuta M, Yagi M, Miyazaki H.

Caries Res. 2006;40(6):487-93.

[Availability of fluoride from meals given to kindergarten children in Brazil.](#)

Buzalaf MA, Pinto CS, Rodrigues MH, Levy FM, Borges AS, Furlani TA, da Silva Cardoso VE.

Community Dent Oral Epidemiol. 2006 Apr;34(2):87-92.

PMID: 16515672 [PubMed - indexed for MEDLINE]

[Related citations](#)

[Fluoride intake and fractional urinary fluoride excretion of Colombian preschool children.](#)

Franco AM, Saldarriaga A, Martignon S, González MC, Villa AE.

Community Dent Health. 2005 Dec;22(4):272-8.

[Total fluoride intake in children aged 22-35 months in four Colombian cities.](#)

Franco AM, Martignon S, Saldarriaga A, González MC, Arbeláez MI, Ocampo A, Luna LM, Martínez-Mier EA, Villa AE.

Community Dent Oral Epidemiol. 2005 Feb;33(1):1-8.

[Fluoride content in bottled waters, juices and carbonated soft drinks in Mexico City, Mexico.](#)

Jimenez-Farfan MD, Hernandez-Guerrero JC, Loyola-Rodriguez JP, Ledesma-Montes C.

Int J Paediatr Dent. 2004 Jul;14(4):260-6.

[Total and acid-soluble fluoride content of infant cereals, beverages and biscuits from Brazil.](#)

Buzalaf MA, de Almeida BS, Cardoso VE, Olympio KP, Furlani Tde A.

Food Addit Contam. 2004 Mar;21(3):210-5.

[Fluoride, calcium and magnesium intake in children living in a high-fluoride area in Ethiopia. Intake through food.](#)

Malde MK, Zerihun L, Julshamn K, Bjorvatn K.

Int J Paediatr Dent. 2004 May;14(3):167-74.

[Fluoride intake from foods, beverages and dentifrice by children in Mexico.](#)

Martínez-Mier EA, Soto-Rojas AE, Ureña-Cirett JL, Stookey GK, Dunipace AJ.

Community Dent Oral Epidemiol. 2003 Jun;31(3):221-30.

[Fluoride content of infant foods in Brazil and risk of dental fluorosis.](#)

Buzalaf MA, Granjeiro JM, Duarte JL, Taga ML.

ASDC J Dent Child. 2002 May-Aug;69(2):196-200, 125-6.

[Fluoride intake in Japanese children aged 3-5 years by the duplicate-diet technique.](#)

Murakami T, Narita N, Nakagaki H, Shibata T, Robinson C.

Caries Res. 2002 Nov-Dec;36(6):386-90.

[\[Fluoride intake by children from water and dentifrice\]](#)

Lima YB, Cury JA.

Rev Saude Publica. 2001 Dec;35(6):576-81. Portuguese.

[Total fluoride intake and urinary excretion in German children aged 3-6 years.](#)

Haftenberger M, Viergutz G, Neumeister V, Hetzer G.

Caries Res. 2001 Nov-Dec;35(6):451-7.

[Fluoride content of foods made with mechanically separated chicken.](#)

Fein NJ, Cerklewski FL.

J Agric Food Chem. 2001 Sep;49(9):4284-6.

[Fluoride content of infant formulas and market milk in Turkey.](#)

Ataç A, Altay N, Olmez S.

Turk J Pediatr. 2001 Apr-Jun;43(2):102-4.

[\[Fluoride intake and excretion in children of Hermosillo, Sonora, Mexico\]](#)

Grijalva-Haro MI, Barba-Leyva ME, Laborín-Alvarez A.

Salud Publica Mex. 2001 Mar-Apr;43(2):127-34. Spanish.

[Fluoride content of infant formulas prepared with deionized, bottled mineral and fluoridated drinking water.](#)

Buzalaf MA, Granjeiro JM, Damante CA, de Ornelas F.

ASDC J Dent Child. 2001 Jan-Feb;68(1):37-41, 10.

Page 7, third paragraph, section 2. Exposure from Foods and Beverages, Subsection 2.1.1. Sample preparation states that "Several authors have described procedures for quantifying fluoride in food matter that do not involve ashing, but these procedures are in a distinct minority". I suggest the reference to these procedures being a minority is removed.

Page 120 ,first paragraph, subsection 8.2. Estimates of Tolerable Upper Limit Exposures. Should the abbreviation UF be UL? If not, it needs to be defined, since this is the first mention

Page 127, last paragraph of the document states that very mild or mild fluorosis is associated with decreases in tooth decay. I suggest this sentence is modified to say appears to decrease tooth decay.

2. Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.

Page 11, second paragraph, section 2. Exposure from Foods and Beverages, Subsection 2.1.4. Confidence in Analytical Results states that “... investigators are keenly aware of technology limitation”. I would add that although they are aware not much progress had been made. I would cite the recommendations made by the NIH to address this issue (see reference below) their subsequent funding of grant R21 DE 14716-1 Development of Gold Standard Methods for Fluoride Analysis, and the studies that have shown there is a need for standardization (see reference below)

[A comparison of results of fluoride determinations by different laboratories.](#)

Mthethwa MT, du Plessis JB.
SADJ. 2005 Jul;60(6):238-40.

[Research needs workshop report: International collaborative research on fluorides.](#)

Clarkson JJ, Hardwick K, Barmes D.
J Dent Res 2000;79:893-904..

Page 11, fourth paragraph, section 2. Exposure from Foods and Beverages, Subsection 2.1.4. Confidence in Analytical Results states that “... colorimetric procedures exhibited sufficient precision. Sufficient precision needs to be defined.

Page 33, fourth paragraph, section 2.2 Natural Fluoride in Solid Foods, subsection 2.2.3. Summary of the Data on Fluoride in Solid Foods states that “It is difficult to tell if changes in analytical methods over time have influenced the results form studies of fluoride in foods.” I would suggest changing it to say: “Results of studies comparing different modifications to methods for fluoride analysis suggests that changes n analytical methods most likely have influenced” The previously mentioned literature, plus the following abstracts from the NIH funded grant previously mentioned support this statement:

E.A. Martinez-Mier, J. Cury, J. Heilman, S.M. Levy, Y. Li, A. Maguire, J. Margineda, D. O’Mullane, P. Phantumvanit, A.E. Soto-Rojas G.K. Stookey, A. Villa, J.S. Wefel, G.M. Whitford, D.T. Zero and V. Zohouri (2004). Development of Standard Fluoride Analytical Methods: Direct Analysis. Caries Res 38;372 (Abstract # 45).

A.E. Soto-Rojas, J. Cury, J. Heilman, S.M. Levy, Y. Li, A. Maguire, J. Margineda, E.A. Martinez-Mier, D. O’Mullane, P. Phantumvanit, G.K. Stookey, A. Villa, J.S. Wefel, G.M. Whitford, D.T. Zero and V. Zohouri (2004). Development of Standard Fluoride Analytical Methods: precision and trueness testing. Caries Res 2004: 38;373 (Abstract # 46).

Soto-Rojas A. E, Martinez-Mier E. A., Margineda J. Development of Standard Fluoride Analytical Methods: Analytical precision of diffusion analysis using different reagents. J Dent Res 83;Special Issue A Abstract # 786 2004 www.dentalresearch.org .

Martinez-Mier EA, Margineda J and Zero DT (2003): Development of standard fluoride analytical methods: calculations of standard curve raw data. J Dent Res 82;B211 (Abstract # 1595).

E.A. Martinez-Mier, J. Cury, A.J. Dunipace, J. Heilman, S.M. Levy, Y. Li, A. Maguire, D. O'Mullane, P. Phantumvanit, G.K. Stookey, J.S. Wefel, G.M. Whitford, D.T. Zero and V. Zohouri (2003): Development of Standard Fluoride Analytical Methods: pilot study. Caries Res 37;291 (Abstract # 70).

Page 113, second paragraph, subsection 6.5 Uncertainty. More detail is needed to explain why slightly above average fluoride intakes are selected. It is implied that this is safety-based, but it needs to be explicitly mentioned

Page 116, second paragraph. Individual variation regarding water intake individual variation should be described. A recent study (see reference below) demonstrated that as much as 33% of infants were given bottle water only for formula reconstitution.

[Children's drinking water: parental preferences and implications for fluoride exposure.](#)

Sriraman NK, Patrick PA, Hutton K, Edwards KS.

Pediatr Dent. 2009 Jul-Aug;31(4):310-5.

- 3. Please consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may for alternative studies that you believe are more representative of exposures.**

Studies are representative, well selected and described. A few additional mentions to references already cited in manuscript are needed.

Page 9, figure 2-1 section 2. Exposure from Foods and Beverages, Subsection 2.1.2. Fluoride Recovery. Comway cell have been substituted by standard Petri dishes as described by Whitford (already cited in manuscript)

The Metabolism and Toxicity of Fluoride

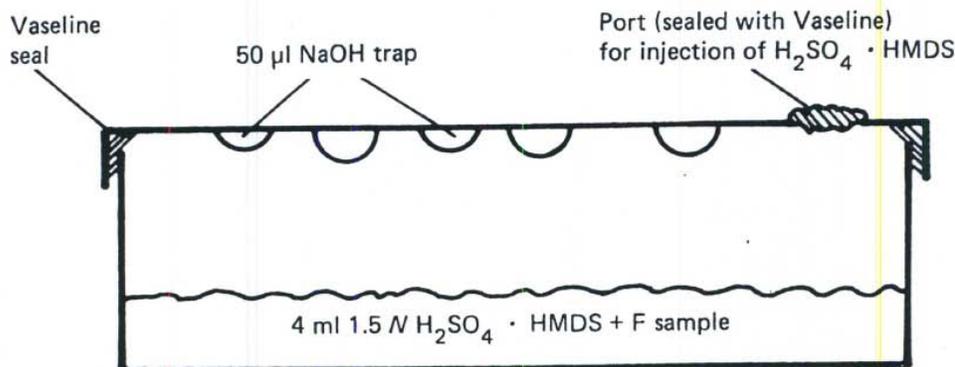


Fig. 13. The essential features of the HMDS-facilitated diffusion method for the isolation of ionic and acid-ionizable fluoride.



Page 9, first paragraph, section 2. Exposure from Foods and Beverages, Subsection 2.1.2. Fluoride Recovery states that HMDS is presumed to accelerate diffusion of fluoride. I suggest the sentence is changed to mention HMDS has been demonstrated to accelerate...” I also suggest a paragraph is added after this describing the most recent modifications to Taves' method, such as those by Dunipace *et al* and Rojas Sanchez *et al* (both already cited in the manuscript).

Page 44, fifth paragraph, section 2.5. Estimates of Dietary Fluoride Intake, subsection 2.5.1. Exposure Assessment Methodologies. I suggest a paragraph is added describing the results of a study that compares different exposure assessment methodologies as they specifically relate to estimation of fluoride in the diet (see reference below)

[Comparison of a dietary survey and the duplicate plate method for determining dietary fluoride ingested by young children: a pilot study.](#)

Martinez-Mier EA, Kelly SA, Eckert GJ, Jackson RD.

Int J Paediatr Dent. 2009 Mar;19(2):99-107. Epub 2008 Dec 11.

Section 4. Fluoride in dental products, subsection on toothpaste. I suggest results for the Iowa fluoride study (already cited in manuscript) for dental fluorosis risk are cited here.

4. Please comment on EPA’s rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically justified and clearly and objectively described? What changes or improvements would you suggest?

The selections are justified, no changes are suggested.

Page 19, second paragraph, section 2.2 Natural Fluoride in Solid Foods, subsection 2.2.1 Fluoride in Infant Foods. The methods used by Singer and Ophaug for fluoride analysis (including preparation of samples should be explained in more detail

Page 71, fifth paragraph, section 2.5. Estimates of Dietary Fluoride Intake, subsection 2.5.5. Combined Estimated for Age Groups of Concern. This bullet point states that “concentration of fluoride appear to be related to food groups as follows: protein foods>grains and vegetables,>fruit,>beverages. I suggest a note is included stating the concentrations in beverages vary widely.

- 5. Please comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication, as supported by the concentrations found in various food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940’s?**

Page 122, third paragraphs subsection 8.2. Estimates of Tolerable Upper Limit Exposures. A clear explanation need to be given why McClure’s data was considered “reasonable basis”, table 2-25 cited here actually states how much McClure results differ from more recent ones. It is my opinion that the results of this study are compromised by the deficiencies in the analytical techniques used at the time. Interferences most likely resulted in reported fluoride concentration in foods lower or higher than actual concentrations. My suggestion would be to compare food item by food item reported by McClure to more recent studies that have utilized more precise methods and obtain some sort of correction factor to account for analytical uncertainties.

- 6. Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.**

All cited references are hyperlinked to abstracts or full text in Pub Med

- 7. Please provide any additional comments and/or further suggestions you may have for improving**

General formatting comment: Description of results of studies should be kept in past tense.

Some other minor editorial comments in the abbreviations include: CDC should sand for Centers for Disease Control and prevention and NIDR, should be changed to NIDCR – National Institute for Dental and Craniofacial Research.

David L. Ozsvath, Ph.D.

1. Describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft document.

In my opinion, the organization of the draft document is fine, and for the most part I found it easy to follow what the authors have written. However, I do have a suggestion for improving the clarity and transparency of Section 8.2, where the 1940-era drinking water exposure estimate is adjusted to account for the exposure from solid food using an “RfD-Equivalent” value. For those who are involved with EPA’s process to revise the MCLG for fluoride, this step is probably very clear; but for an outside reader, it is not intuitive. Much of the confusion I experienced was a result of inconsistent terminology, but I also found that the derivation of “RfD-Equivalents” is not entirely transparent. In my responses to Question 7 below, I provide details about where the text is confusing and how its clarity might be improved.

2. Have the uncertainties associated with the analysis been adequately characterized? Are there any important uncertainties in the data that are not discussed adequately in the document, especially in the synthesis sections? Please describe any concerns you have and any specific suggestions for improving or enhancing the uncertainty discussion.

The uncertainties associated with the data presented in Sections 2 through 5 are adequately characterized, and it is clear from reading these sections that the level of certainty varies between exposure media and age categories. Section 6.5 acknowledges the uncertainty associated with data analysis, but the way in which it is handled (to use “average to slightly above average fluoride intakes for the RSC analysis”) is not justified beyond the statement that the “EPA believes that these are reasonable estimates” (page 113). It would be helpful if a sensitivity analysis was conducted in which RSC values were calculated using the high and low estimates of fluoride intakes from the various exposure media for the different age categories. This would provide a better picture of the effect that uncertainty has on the conclusions.

A secondary point relates to the way in which drinking water fluoride intake is treated as compared to other exposure media. Although the authors have followed EPA protocol in using a 90th percentile water intake to quantify exposure from drinking water, a similar quantification is not possible for other fluoride sources, so estimates of the average intake values are used. This raises the question of whether it is appropriate to compare 90th percentile drinking intake data to mean intake values for other media (Figure 8-1), or if mean intake values should be used for all exposure media (Figure 8-2). For the purposes of this study, it seems that of the approaches which are scientifically defensible, the one that leads to the lowest possible RSC for drinking water is the most appropriate to use.

3. Consider the studies that have been selected as representative of exposures for the specific age groups and/or exposure media. Have these studies been adequately summarized and interpreted? Indicate any deficiencies in the descriptions of the studies and any suggestions you have for improvement. Describe any concerns you have about the selection of these studies, as well as any recommendations you may for alternative studies that you believe are more representative of exposures.

The only exposure media that I am qualified to comment on are drinking water and soil.

Section 3.2 is a rather brief treatment of the natural sources of fluoride in drinking water, and the emphasis is on naturally high concentrations. If the intent had been to develop a representative fluoride

concentration for groundwater in the U.S., then I would expect a more detailed treatment of the subject. However, given the fact that EPA is only addressing regulated drinking water and has a massive ICR database available for analyzing fluoride concentrations in public drinking water supplies, Section 3.2 is adequate as written.

With regards to the ICR data, the authors note on page 82 that the distribution of fluoride concentrations is positively skewed, meaning that means are generally higher than medians for any given quarter or year. In such cases, medians would normally be considered more representative of the dataset than means, but the authors chose to use mean values in their RSC analysis. I assume this was done to avoid underestimating the drinking water contribution; however, the net result is to increase the RSC for drinking water, which also leads to a higher MCLG. Although the effect of choosing mean over median values might not affect the final RSC percentages significantly, I think that some rationale for this decision might be appropriate in the exposure assessment summary (Section 6.2 on page 110).

Unfortunately, there is no comparable database for fluoride concentrations in soil. Section 6.4 (pages 112) uses 400 ppm as an average concentration for fluoride in soil. Based on my understanding of the literature, this is a reasonable number and at least does not underestimate the average concentration (400 ppm is near the high end of most ranges given for average soil concentrations). However, it should also be noted that a 2009 document prepared by The Federal-Provincial-Territorial Committee on Drinking Water (CDW) for Health Canada (link included below under Question 6) used 100 ppm as the average fluoride concentration in soil to estimate daily fluoride intake from soil ingestion, although this value might not apply to the U.S.

I do have one additional comment relative to the question of whether the studies selected are representative. In large part, this document is an updated revision of two chapters from the NRC (2006) report (Chapter 2: Measures of Exposure to Fluoride in the United States, and Chapter 11: Drinking Water Standards for Fluoride). There are some additional studies included in this recent EPA effort, but I noticed that the final relative source contribution (RSC) results are not very different from what is reported in the NRC (2006) document. The fact that two separate teams of scientists came to essentially the same conclusions lends a degree of confidence to the results (the slight differences are within the range of uncertainty that is inherent in this process). However, it should also be noted that the 2009 CDW document cited above (link included below under Question 6) presents daily fluoride intake values that differ more substantially from the values presented by NRC (2006). Although the CDW document is written for a different population, it is worth considering why their conclusions are not more similar to those reported by NRC (2006) and EPA (2010).

4. Please comment on EPA’s rationale for selection of specific data elements to represent average exposures for each of the age groups. Has the selection been scientifically justified and clearly and objectively described? What changes or improvements would you suggest?

This is outside my area of expertise.

5. Please comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication, as supported by the concentrations found in various food groups from more recent analytical data. Do you agree with this approach? If not, what approach would you suggest for estimating food intake for the 1940’s?

The answer to this question is outside my area of expertise, but I noticed on page 34 the authors state that the differences between McClure’s (1943; 1949) data and the more recent USDA (2005) data shown in

Table 2-25 “cast doubt on the results of exposure assessments derived from some of the early food data”. However, in the third paragraph on page 122 the authors cite the same data (in Table 2-25) and state that “McClure’s (1943) estimate for dietary intake based on a diet where solid foods had an average of 0.5 ppm fluoride appears to provide a reasonable basis for the contribution of solid foods to total exposure in the 1940’s.” These statements appear contradictory, but I suspect that the authors intended to cite Table 2-41, not 2-25 on page 122? This issue could use some clarification.

6. Provide citations (and, if possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added.

Beltran, E.D., Griffin, S.O., and Lockwood, S.A. 2002. Prevalence and trends in enamel fluorosis in the United States from the 1930s to the 1980s; *Journal of American Dental Association*, 133(2):157-165. <http://jada.ada.org/cgi/content/full/133/2/157>

Federal-Provincial-Territorial Committee on Drinking Water. 2009. Fluoride in Drinking Water <http://fluoridealert.org/canada.2009.report.pdf>

Ismail, A.I, and Hasson, H. 2008. Fluoride supplements, dental caries and fluorosis: A systematic review; *J. Am. Dent. Assoc.* 139:1457-1468. <http://jada.ada.org/cgi/reprint/139/11/1457>

7. Please provide any additional comments and/or further suggestions you may have for improving the document.

I have a number of comments/questions/suggestions, which are listed chronologically below.

(1) The first paragraph under Section 1.2 (on page 3) states that the fluoride MCLG was derived using an estimated 20 mg/day chronic exposure. I think that it would be helpful to explain or mention where this 20 mg/day value comes from.

(2) Page 9 (in the third paragraph) is the first place I noticed the use of “mg F/kg” as a concentration, and page 13 (in the first paragraph) is the first place I noticed the use of “mg F/L” as a concentration. There is nothing wrong with using these units; however, in other places concentrations are expressed as “mg/kg” and “mg/L” (the authors switch back and forth throughout the document). I think that consistency would be preferable.

(3) A minor point regarding Section 2.1.3 (starting on page 9): Unless there is some reason for organizing this section as they have, I think that it makes more sense to present the fluoride measurement techniques in the order in which they were invented.

(4) The second sentence of the second paragraph on page 17: I don’t believe that “optimum fluoride” has been defined yet in this document, although most of its readers would probably know what this means.

(5) Fourth paragraph on page 32: Raisins are classified as an outlier because their fluoride content reflects the use of cryolite as a pesticide. This issue comes up again later in the document, and I think that it might be helpful to establish right away (on page 32) the fact that fluoride inputs from pesticides will be

treated separately. Otherwise it seems to the reader that this potentially important exposure pathway is going to be ignored.

(6) Table 2-26 (on page 35): “Hargraeves” is misspelled in the footnote. The authors should check the spelling on this name throughout the document, as I believe there are at least two other places where it is misspelled (for example, see the second paragraph on page 38).

(7) I believe that the caption for Figure 3-1 on page 76 should cite Fleischer et al., 1974, not 1972.

(8) The last sentence in the first paragraph at the top of page 82 (i.e., “There were only 6 entries in the data set that reported concentrations between 40 and 100 mg/L, and 420 greater than or equal to 100 mg/L.”) is slightly ambiguous. Are the authors saying that 420 entries reported concentrations equal to or greater than 100 mg/L? I assume that the purpose of this sentence is to state how many entries were eliminated from the data set because their concentrations were considered anomalously high? Perhaps this sentence could be written as: “A total of 426 entries were considered anomalously high and eliminated from the database: 6 values between 40 and 100 mg/L, and 420 values greater than or equal to 100 mg/L”?

(9) The second sentence in Section 4.3 (on page 98) reads: “With few exceptions all of these studies were published after in the early to mid-1990s and are likely to not reflect changes in guidance on the amounts of toothpaste recommended for brushing (a pea-sized portion rather than a ribbon).” I believe that the word “after” should be deleted from this sentence (to read: “... published in the early to mid-1990s...”).

(10) The last paragraph on page 114 states that 90th percentile drinking water intakes are used for infants and children up to age 14 and 2 L/day is used for individuals over age 14 because this is the 90th percentile value for adults. I’m not sure why the authors do not simply state that the 90th percentile water intake is used for all ages. By wording it as they do, it initially sounds as though the individuals above age 14 are treated differently from the younger population. In fact, footnote “a” for Table 7-1 reinforces this idea.

(11) The second sentence in the first paragraph on page 116 states: “It is apparent that, for most individuals in the population, the contribution from drinking water has decreased considerably from the 100% assumed in the EPA 1986 derivation of the MCLG for crippling skeletal fluorosis.” Actually, the data in Figure 7-1 do not show that the contribution has necessarily decreased since 1986 but only that it is less than the 100% assumed by EPA in 1986.

(12) The second paragraph on page 117 begins with the statement, “Geologically, one-third to one-half of the U.S. has access to ground water containing less than 0.5 ppm fluoride...”, but the next sentence states that “69% of the U.S. population receives fluoridated water” (between 0.7 and 1.2 mg/L). I realize that the percentages in the first sentence do not refer to the proportions of the population that actually consume low fluoride water, but the juxtaposition of these two statements is somewhat confusing. Perhaps the second sentence could begin with, “However,” to help make the point that is then more overtly stated in the third sentence.

(13) The value of 0.07 in Table 8-2 (on page 121) is shown in bold, perhaps because the EPA chose to use this dose estimate as the contribution from drinking water in 1942? There should be a footnote to the table that explains the bold font.

(14) The first sentence in the third paragraph on page 122 (which mentions that the OW increased the 0.07 mg/kg/day dose for drinking water by 0.01 mg/kg/day to account for exposures from food in the 1940’s) is confusing to someone who has not read the EPA (2009a) document, because the implication

from Section 1.1 (especially the paragraph that begins at the bottom of page 2) is that no attempts have been made in the past to account for fluoride exposure from sources other than drinking water. This notion is then reinforced when one reads Section 1.2 and the first paragraph on page 116. It would be helpful if Section 1.1 made it clear that EPA (2009a) has already made an estimate of the fluoride exposure from food but that the current study will re-evaluate that estimate in light of additional information (or in a more scientifically defensible manner, etc.).

(15) Figures 8-1 through 8-3 include a plot of the Pre-Peer Rev (or Proposed) RfD, but this is actually the RfD multiplied by the body weight (also referred to as the “daily intake equivalent”, the “RfD-based daily intake limit”, the “RfD-Equivalent” and the “OW RfD-equivalent” in the text). It would help clarify the text, Table 8-4, and the graphs if only one term is used consistently in both text and graphs. Also, I assume that the “Pre-Peer Rev Rfd” curve in Figures 8-1 through 8-3 is terminated at the 7 to <11 years column to keep the vertical scale less than 3.5, but it would help to explain this in a footnote.

(16) In addition to the confusion created by using different terms to refer to the same variable, the text is not clear why the “RfD-Equivalent” values in Table 8-4 on page 123 (which are referred to as “RfD-based intake limit” in the equation used to calculate them) are being calculated. In the last paragraph on page 122 the reader is told that the McClure (1943) data support the 0.01 mg/kg/day fluoride contribution from solid food that was assumed by EPA (2009a), but there is no transition from this statement to the derivation of “RfD-Equivalent” values. It would help if this process were explained more explicitly. For example, the first paragraph on page 123 could be rewritten: “Therefore, an estimate of the total fluoride exposure at the time of Dean’s 1942 study was made by adjusting the reference dose (OW RfD) from 0.07 mg/kg/day (the estimated exposure from drinking water) to 0.08 mg/kg/day to include the exposure from solid food during the 1940s. This OW RfD (or Rfd) was converted to a daily intake equivalent (or whatever term the authors prefer) by multiplying the mean body weights for each of the age groups of concern using the following equation:”

(17) In Table 8-4 (on page 123), right-hand parentheses are needed for the words “skeletal fluorosis” in the rows for “Adult females” and “Adult males”.

(18) I think that it would improve the document’s clarity and transparency if Section 8 concluded with a summary of how the study objectives were met. The way the current documents ends is somewhat abrupt, and there are no recommendations or explicit statements about how the conclusions will be used (although I am certain that the authors understand how their findings fit into the flow of what the EPA is doing to address fluoride drinking water standards).

**Appendix G:
EPA Slides Presented at the
Peer Review Meeting**

Fluoride Exposure and Relative Source Contribution (RSC) Assessment

EPA Office of Water
External Peer Review Meeting
May 14, 2010

Do Not Cite, Quote or Distribute
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Background

Year	Event
2003	EPA requested NRC to evaluate the health effects and occurrence of fluoride in public water supplies
2006	NRC Report Published: Recommended a dose-response analysis for severe dental fluorosis and skeletal effects. Recommended an extended evaluation of exposure to sensitive populations . Advised EPA to wait for the publication of an ongoing study of osteosarcoma. The study has not yet been published.
2008	Completed and peer reviewed the dose-response analysis. Reviewers agreed with Dean (1942) as the critical study. Suggested modeling severe dental fluorosis to a lower response level (0.5% vs. 1%).
2010	Completed the peer review draft of the Exposure and Relative Source Document (June).

Next Steps

- Address peer review comments and revise the Exposure and RSC Report.
- Post the Dose-Response and Exposure/RSC Reports on the Web with peer review comments and EPA responses – June 2010
- OGWDW begins consideration of revisions to the MCLG/MCL
 - SDWA Statutory Mandate:
 - The Administrator shall, not less often than every 6 years, review and revise, as appropriate, each national primary drinking water regulation.
 - Any revision to an NPDWR shall maintain, or provide for greater, protection of the health of persons.

Differences between the MCL and MCLG

- MCLG is not enforceable
 - Based on the NRC report as the description of hazard and the EPA Dose-Response Assessment
- MCL enforceable
 - Considers analytical and technological limitations
 - Considers relationship of the costs involved in requiring systems to comply with the MCLG compared to the benefits realized by doing so.

RSC and the MCLG: General Policies

- Determine a Reference Dose
 - Determine the Drinking Water Equivalent Level (DWEL) from the RfD
 - **DWEL = RfD x body weight ÷ drinking water intake**
 - Based on body weights and 90th percentile drinking water intakes for sensitive populations (children in the case of fluoride)
 - OW could potentially use the BMDL from the dose-response as the DWEL
 - Calculate an MCLG that is protective for the persons served by public water systems
 - **MCLG = DWEL x RSC**
 - Could use each age group and its RSC and choose the limiting value
 - Could normalize body weight and drinking water intakes across the sensitive age range and apply the RSC to the normalized value
-

Generalized Assessment Findings

- Exposure estimates indicate that the RfD is being exceeded for some drinking water consumer age groups at an average drinking water fluoride concentration of 0.9 mg/L
 - Prevalence of dental fluorosis in the population among the population has increased from ~10% in the Dean Study to >32% in 2000
 - Monitoring of the population demonstrates that there are individuals with severe dental fluorosis in the United States
 - The dose-response data are supportive of an increased risk of cavities if dental fluorosis is severe (age independent)
 - Cavities are an adverse health effect with consequences if left untreated
 - >4,000 public drinking water systems have fluoride concentrations greater than the average concentration of 0.9 mg/L (mostly ground water systems).
-

Iowa Fluoride Study Data

- 622 children –mostly moderate to high socioeconomic status
 - Reporting of intakes of water beverages selected foods supplements and dentifrice by parents from birth to 48 months (3-4 month intervals)
 - Teeth examined at ages 8-10 (mean 9.2 years).
 - Fluorosis prevalence
 - 8 cases categorized as severe fluorosis; one had enamel pits (central incisors and first molars (0.2%)
 - Affected child’s average intake 9 through 36 months was 0.075 mg/kg/day and 0.079 mg/kg/day for 16 through 36 months. Apparently breast fed until sometime between 6 and 9 months.
 - Pictures for one other case could not be located – fluoride intake high at 6 and 9 months with limited reporting thereafter
 - Fluorosis scale used categorized severe fluorosis as severe staining and/or pitting of the enamel
 - No severe dental fluorosis cases for a Fluoride exposure less than 0.06 mg/kg/day
-

**Appendix H:
Panel Chair’s Summary of
Reviewer Pre-Meeting Comments**

External Peer Review for Fluoride: Exposure and Relative Source Contribution Analysis

Summary of Reviewers Comments

Provide suggestions for improving the clarity, organization, and/or transparency of the draft document

- ▶ Reorganization and inclusion of an overview are needed
- ▶ *Summary of how the study objectives were met is needed*
- ▶ Statement of purpose/problem and clear statements on the impact of specific datasets
- ▶ Road map, description of approach would be helpful
- ▶ Overview of challenges is needed
- ▶ *Clarification on MCLG, RSC and RfD is needed*
 - ▶ *Explanation of origin of 20 mg/day values used to calculate MCLG is needed*
- ▶ Use of tables to summarize information and flowcharts to explain approach
- ▶ Reference to US EPA document

▶

Provide suggestions for improving the clarity, organization, and/or transparency of the draft document

- ▶ Rearrangement of information, earlier references to and rationale for choice of critical data sets
- ▶ Chapter 8 particularly hard to follow / Chapter 2 would benefit from updated information on analytical methods
- ▶ Standardize terminology and units
 - ▶ *Explanations for choice of units and conversion are needed for beverages and foods*
 - ▶ *Nomenclature for SEM is inconsistent*
 - ▶ *Use of mg F/kg - mg F/L -mg/kg -mg/L” (the authors switch back and forth throughout the document)*
 - ▶ *Use of RfD - daily intake equivalent - RfD-based daily intake limit - RfD-Equivalent - OW RfD-equivalent*

Indicate concerns and any specific suggestions for improving or enhancing the uncertainty discussion

- ▶ Lack of quantification and estimation of uncertainty
- ▶ Lack of clarity on selection of average values
- ▶ RSC uncertainty needs to be addressed
- ▶ Discussion on dynamic nature of fumigant market is needed
- ▶ Uncertainty related to the use of CSFII should be discussed
- ▶ Uncertainty related to DWI and choice of 90th percentile needs to be further discussed
- ▶ Discussion of uncertainty specific to key data set should be expanded
- ▶ Discussion of analytical uncertainty should be expanded
- ▶ Sensitivity analysis would be helpful (RSC values calculated using high and low estimates of fluoride intakes)

Indicate deficiencies in the descriptions of the studies selected as representative and any suggestions you have for improvement. Recommendations for alternative studies

- ▶ Inadequate information about food studies (more information needed on consumption rates)
- ▶ *Representativeness of studies limited on a few individual or geographic areas is questionable*
- ▶ Explanation for choice of studies is needed
- ▶ Suggestion for alternative approach – USDA fluoride database coupled with CSFII – Collaboration with ORD
- ▶ More information on quality of various exposure methodologies is needed
- ▶ Choice of mean over median for ICR data needs to be further explained
- ▶ Specific suggestions for studies to be added to specific sections are offered
- ▶ Comparison to the CDV Federal-Provincial-Territorial Committee on Drinking Water (CDW) for Health Canada is needed
- ▶ *Hospital study by Taves is not likely to be representative of adult food intakes*
- ▶ *Singer study is likely not representative of current dietary intake patterns*

Is selection of specific data elements to represent average exposures for each of the age groups scientifically justified and clearly and objectively described?

- ▶ Selection of age groups needs further discussion
 - ▶ *Not clear if age groups are similar for underlying cited studies and summary table (6.1)*
- ▶ The average food exposure for infants is probably too high
 - ▶ *Insufficient data describing Ophaug study to examine relevance for youngest age class*
- ▶ The average drinking water exposure for infants is probably too high
- ▶ The discussion of the contribution of sulfuryl fluoride to dietary exposure from food is difficult to follow
 - ▶ *There are multiple sulfuryl fluoride issues*
- ▶ Estimation of total exposure need to be revisited (*bias related to use of 90th percentile drinking water exposure and average food consumption*)
- ▶ Text on the criteria used to identify the key data/studies is needed
- ▶ Methods used for fluoride analysis need further description
- ▶ Better description of variations in fluoride concentration in specific food groups (for example beverages) is needed

Comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication. Suggest alternative approach for estimating food intake for the 1940’s

- ▶ Mc Clure data appears to overestimate fluoride concentration when compared to USDA 2005 data. Not clear why it is later stated this comparison provides confidence in the McClure data
 - ▶ Background on the need to estimate the fluoride concentration from the 1940’s is needed
 - ▶ Discussion of the dental fluorosis response from Dean’s studies needs to be provided and further explanation on the dose response analysis is needed
 - ▶ More detail is needed to explain the importance of McClure data in chapter 8 (section 8.2 is particularly confusing)
-

▶

Comment on the validity of basing the food intake estimate for the 1940’s on the McClure (1943) publication. Suggest alternative approach for estimating food intake for the 1940’s

- ▶ Some type of quantitative uncertainty analysis needs to be performed to address limitations of using McClure data
 - ▶ Differences in age groups and body weights between Dean and McClure raise concern
 - ▶ The role of the McClure data in the derivation of RfD needs to be better explained
 - ▶ Selection of 0.5 ppm as estimate for fluoride in solid foods needs be better explained
 - ▶ Analytical techniques used in the McClure study compromise results, they may over or underestimate (due to interferences)
-

Citations

- ▶ Provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA should consider adding to the document, and describe where you suggest these references be added
- ▶ Refer to pre-meeting comments

Provide additional comments and/or further suggestions for improving the document

- ▶ Not clear if age groups are similar for underlying cited studies and summary table (6.1)
 - ▶ Use of term intake needs further clarification
 - ▶ Cross reference in tables is confusing and sometimes incorrect
 - ▶ Insufficient data describing Ophaug study – there are multiple questions related to his methods and calculations and adequacy of use for several age groups
 - ▶ Multiple questions related to Van Winkle study and its combination with the Ophaug study
 - ▶ Bias related to use of 90th percentile drinking water exposure and average food consumption
 - ▶ Representativeness of studies limited on a few individual or geographic areas is questionable (concerns raised over Jackson et al study)
 - ▶ Confusion between upper bound on consumption with an upper bound on contaminant concentration needs to be addressed
-

Provide additional comments and/or further suggestions for improving the document

- ▶ Hospital study by Taves is not likely to be representative of adult food intakes
- ▶ Singer study is likely not representative of current dietary intake patterns – multiple assumptions need to be revisited
- ▶ Assuming 0.5 < y year group ingests no beverages is incorrect
- ▶ Treatment of beverages for the other age classes is confusing
- ▶ There are multiple sulfuryl fluoride issues (see pre-meeting comments)



Provide additional comments and/or further suggestions for improving the document

- ▶ Description of IRB status for studies described
- ▶ Explanations for choice of units and conversion are needed for beverages and foods
- ▶ Nomenclature for SEM is inconsistent
- ▶ Table 2-50 is of limited use
- ▶ Definition of term SMCL is needed
- ▶ Recent reference for temperature dependant concentrations for fluoride is needed
- ▶ Term margin of exposure is incorrectly used
- ▶ RfD interpretation of exposures is incorrect



Provide additional comments and/or further suggestions for improving the document

- ▶ *Explanation of origin of 20 mg/day values used to calculate MCLG is needed*
 - ▶ *Need to present analytical techniques in order of development*
 - ▶ *Optimum fluoride level needs definition*
 - ▶ *Need to mention fluoride input from pesticides will be treated separately*
 - ▶ *Several spelling mistakes were identified*
 - ▶ *Several mistakes in captions for figures were identified*
 - ▶ *Consistent style is needed (suggest past tense)*
 - ▶ *Some abbreviations are incorrect*
 - ▶ *Specific style suggestions were offered*
 - ▶ *Issues associated to RfD - daily intake equivalent - RfD-based daily intake limit - RfD-Equivalent - OW RfD-equivalent*
-

▶