EPA Dose-Response and Exposure Assessments for Fluoride

EPA Office of Water
National Oral Health Conference
Pittsburgh, PA
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Topics Covered

- Regulatory Background
- Major Outcomes
- Dose Response
- Reference Dose (RfD)
- Exposure
- Relative Source Contribution (RSC)
- RfD -Exposure Relationship

Drinking Water Standard History

- **1986 - Existing Drinking Water Standards**
  - Established MCLG /MCL of 4.0 mg/L to protect against crippling (stage 3) skeletal fluorosis
  - Set Secondary MCL (SMCL) at 2.0 mg/L to protect against objectionable (moderate/severe) dental fluorosis (not enforceable but public notification required).
- **1996 – Safe Drinking Water Act**
  - Required review of Drinking Water Standards every six years.
- **2003 – Finalized "first" review of drinking water standards**
  - No revision appropriate at that time
  - Requested National Academies of Science National Research Council (NRC) review
- **2010 – Finalized the "second" review of drinking water standards**
  - No revision appropriate because dose-response assessment on the noncancer effects of fluoride and evaluation of the relative contribution of fluoride in drinking water were not complete.
- **2011 – The OW released the Dose-response and Exposure Assessments**
  - Documents support the proposal to withdraw the Office of Pesticide Programs (OPP) tolerances for sulfuryl fluoride. Comments can be submitted to the OPP docket.

NRC 2006 Report

- **Review requested and funded by EPA**
  - Result of the first Six-Year Review of Drinking Water Standards
- **NRC Report**
  - **Dental Fluorosis** - Most panel members concluded "severe dental fluorosis" is an adverse effect (due to thinning/pitting of the tooth enamel); 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; Wait for publication of two Harvard osteosarcoma (bone cancer) studies*
- **NRC recommendations to EPA**
  - ***Update the dose-response assessment***, consider susceptible populations, characterize uncertainties/variability
  - ***Update the exposure assessment***

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

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
    - **Released January 7, 2011**
  - Exposure and Relative Source Contribution
    - **Released January 7, 2011**
  - Relationship of Fluoride to Cancer
    - To be initiated after publication of Harvard study as recommended by NRC (2006)*
- Initiate **review** to determine whether to initiate steps to revise the standard.
  - Review process considers health, treatment technology, analytical methods, occurrence, etc.
  - No timeframe yet for finalizing review effort
- Develop guidance for water systems that fluoridate

*Only one of the two Harvard studies has been published to date.

What the Assessments Changed

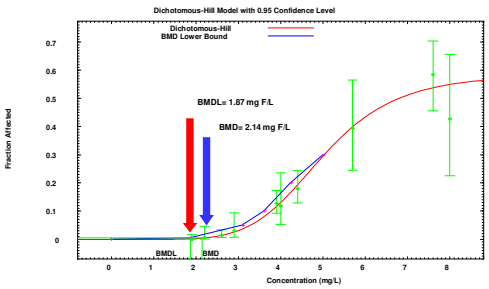
- The Critical Effect changed from crippling skeletal fluorosis to severe dental fluorosis supported by skeletal effects
  - The drinking water concentration associated with severe dental fluorosis before fluoridation is ~2 mg/L
- The proportion of total fluoride exposure that currently comes from drinking water (Relative Source Contribution) decreased to 40 to 70% depending on the age group*
  - Nationally, total fluoride from all exposure sources appears to have increased from the time fluoridation of drinking water was first initiated.
    - Commercial use of fluoridated water in processing foods and preparing commercial beverages
    - Fluoride in toothpaste ingested by young children
    - Sulfuryl fluoride

*When EPA established MCLG/MCL of 4.0 mg/L, assumed all exposure from drinking water (i.e., 100% RSC).

Dose-Response Critical Study

- Dean (1942) – Severe Dental Fluorosis
- 5,558 children - mostly ages 10-12
  - Younger age children only from locations with the highest F drinking water concentration
  - Life-long residents
- 21 locations
  - Bauxite, AK not included because of aluminum mine and smelter
- Drinking water concentrations: 0 – 8.0 mg/L
  - 18/21 values were averages for 12 months
  - Method colorimetric; some interference by other ions possible

Benchmark Modeling of the Dean Data



The BMDL is the statistical estimate for the drinking water concentration in the 1930's where the fluoride in the water lead to severe dental fluorosis in 0.5 % of the population at the lower bound 95% confidence level.

Model Outcome Stable

Dichotomous-Hill Model Variation	BMD mg/L	BMDL mg/L
Base Model	**2.14**	**1.87**
2 high dose sites eliminated	2.16	1.85
2 high altitude sites eliminated (were also the two lowest concentrations with a response)	2.19	1.75
2 high temperature sites eliminated	2.15	1.86
2 high altitude and 2 high temperature sites eliminated	2.20	1.73

BMD results relatively stable; BMDL impacted by the decrease in the population size when some localities were removed from the analysis

Reference Dose Challenges

- Point of Departure from the Benchmark Dose analysis is a concentration in drinking water not an exposure.
- Exposures occurred 70 to 80 years ago
  - Exposures nearly exclusively water and diet
  - No fluoridation or fluoridated toothpaste
- No data on drinking water intakes at the time
- Dietary data from the era based on colorimetric analyses subject to interference from food components

EPA Approach

- Body Weight and Drinking Water Intake data from Ershow and Cantor (1989)
  - 1977-1978 USDA Food Consumption Survey
  - Age groups from six months to 14 years (Massler and Schour, 1958)
    - Recommended by the American Dental Association
    - Development of the 3rd molars included
- Dietary Estimate from McClure (1943) adjusted using fluoride concentration data from USDA (2005)
  - McClure (1943) body weight for the age groups
- Accept IOM (1997) Adequate Intake (AI) as reflecting doses with nutritional benefit
- Calculate doses using mean to 95th percentile drinking water intakes

Dose Estimate Results – Drinking Water

Dose Estimates (mg/kg/day)				
Age (yr)	mean	75%	90%	95%
0.5-<1	**0.07**	0.10	0.14	0.16
1 -<4	0.09	0.10	0.15	0.19
4-<7	**0.07**	0.09	0.12	0.14
7-<11	**0.05**	0.06	0.08	0.10
11-14	**0.04**	**0.05**	0.06	0.08

0.07 mg/kg/day = selected as drinking water contribution dose at the BMDL
Values **≤ 0.05 mg/kg/day** eliminated from consideration because at or below IOM (1997).
A Range of values provided for use by risk managers (peer reviewer recommendation)

RfD Derivation

RfD = $\frac{\text{POD}}{\text{UF}} = \frac{0.08 \text{ mg/kg/day}}{1} = 0.08 \text{ mg/kg/day}$

Where:

POD = Point of Departure = BMDL dose (0.07 mg/kg/day) + Diet Dose (0.01 mg/kg/day)

UF = Uncertainty Factor = 1

Confidence in RfD Medium

Experimental Support (Iowa Fluoride Study):

- 8 from 579 from children had severe dental fluorosis based on the Fluorosis Risk Index (includes staining and/or pitting).
  - 1 child with pits average intake 16 to 36 months = 0.079 mg/kg/day
  - 6 lacked pitting average intakes > 0.06 mg/kg/day
  - No pictures for one child

Office of Water RSC Policy

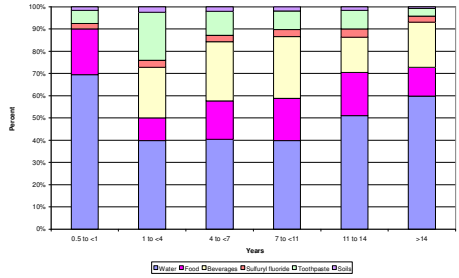
- Mean values for all exposures except drinking water
- Drinking Water Intakes based on average fluoride concentration and 90th Percentile drinking water intakes (consumers only)

RSC = $\frac{\text{Exposure from drinking water (mg/day)}}{\text{Total exposure (mg/day)}}$

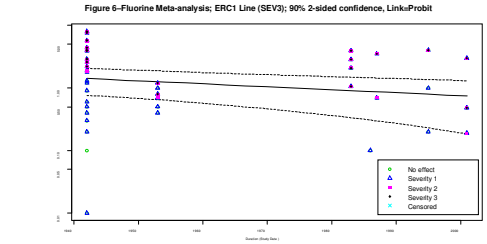
Quantitative RSC analysis

- Included Exposures
  - Ingested tap water – Fluoride concentration 0.87 mg/L
    - National average for systems detecting fluoride
  - Solid foods
  - Beverages
  - Ingested toothpaste
  - Soils
- Excluded exposures
  - Inhalation of ambient air - A minor quantitative contributor
  - Mouthwash – No data
  - Dietary supplements for children
    - Use not recommended when drinking water fluoridated
  - Products used on an occasional basis
    - Fluoride-containing pharmaceuticals
    - Dental fluoride treatments

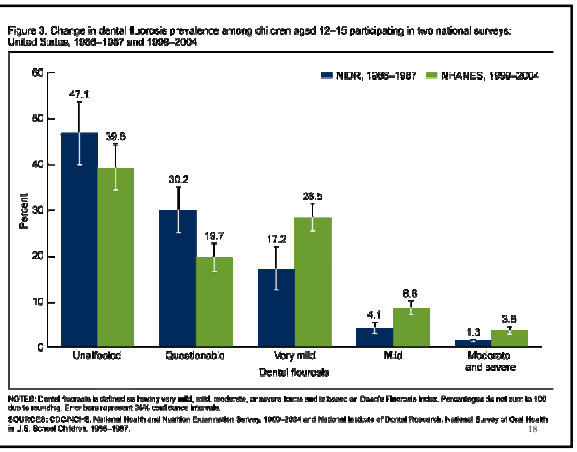
Age Specific RSC Outcome



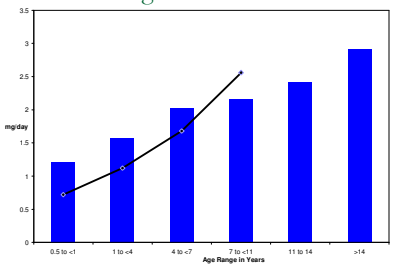
Categorical Regression Analysis: Date of Study as the Variable



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.

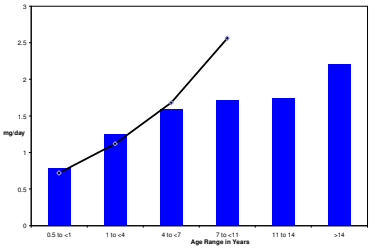


Exposure Estimates Relative to the RfD: 90th Percentile Drinking Water Intake



Mean Water Concentration = 0.87 mg/L using the 90th percentile drinking water intake for consumers only. Other exposure estimates are average values; RfD based on a severe fluorosis prevalence of ≤ 0.5% of the population exposed during the period of vulnerability

Exposure Estimates Relative to the RfD: Average Drinking Water Intake



Mean water Concentration = 0.87 mg/L; mean drinking water intake