Fluoride in Drinking Water: A Scientific Review of EPA’s Standards

Committee on Fluoride in Drinking Water
Board on Environmental Studies and Toxicology
Division on Earth and Life Studies
National Research Council

March 21, 2006
• MCLG – maximum contaminant level goal
  - level of a contaminant in drinking water below which there is no known or expected risk to health
  - non-enforceable public health goal

• MCL – maximum contaminant level
  - highest level of a contaminant allowed in drinking water
  - enforceable standard
  - set as close as feasible to the MCLG; technology and costs are considered
Definitions

• SMCL – secondary maximum contaminant level
  - non-enforceable guideline for managing drinking water for aesthetic, cosmetic (e.g., tooth discoloration), or technical effects
• 1986
  - MCLG and MCL set at 4 mg/L to protect against “crippling” skeletal fluorosis
  - SMCL set at 2 mg/L to reduce occurrence and severity of “objectionable” enamel fluorosis.

• 1993
  - MCL reviewed by NRC in 1993
  - 4 mg/L is appropriate as an interim MCL
  - More research needed on fluoride intake, enamel fluorosis, bone strength and fractures, and carcinogenicity.
• 2001
  - EPA requests review of MCLG and SMCL for fluoride as part of the requirement under the Safe Drinking Water Act to periodically reassess the adequacy of the drinking water standards.
Statement of Task

- Review toxicologic, epidemiologic, and clinical data on fluoride, particularly data conducted since 1993 NRC report.

- Review exposure data on orally ingested fluoride from drinking water and other sources (e.g., food, toothpaste).

- Evaluate the scientific basis of the MCLG and SMCL and their adequacy to protect children and others from adverse health effects.

- Consider relative contribution of various fluoride sources to total exposure.

- Identify data gaps and recommend research relevant to setting the MCLG and SMCL.
Statement of Task

- Issues outside the scope of the task:
  - water fluoridation guidelines (0.7-1.2 mg/L)
  - benefits of fluoride
  - economics
  - water-treatment technology

- Study sponsor: U.S. EPA
Committee Roster

- **John Doull (Chair)**, University Kansas Medical Center, Kansas City
- **Kim Boekelheide**, Brown University, Providence, RI
- **Barbara Farishian**, Washington, DC
- **Robert Isaacson**, Binghamton University, Binghamton, NY
- **Judith Klotz**, University of Medicine and Dentistry of New Jersey, Piscataway
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- **Charles Poole**, University of North Carolina, Chapel Hill
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- **Nu-May Ruby Reed**, California Environmental Protection Agency, Sacramento
- **Kathleen Thiessen**, SENES Oak Ridge, Inc., Oak Ridge, TN
- **Thomas Webster**, Boston University, Boston, MA
NEW DATA THAT FILL GAPS IDENTIFIED IN 1993 REPORT
- Fluoride intakes
- Prevalence of enamel fluorosis
- Bone fractures
- Carcinogenicity

OTHER NEW DATA
- Pharmacokinetic models that predict fluoride accumulation into bone
- Reproductive and developmental toxicity
- Neurotoxicity and neurobehavior
- Endocrine effects
- Effects on gastrointestinal, renal, hepatic, and immune systems
### Drinking Water Contribution to Total Exposure

**Drinking Water – Natural Sources**
- 2.0-3.9 mg/L (1.4 million people exposed)
  - 57% - 90% for average individual
  - 86% - 96% for high-water intake individual
- ≥ 4mg/L (200,000 people exposed)
  - 72% - 94% for average individual
  - 92% - 98% for high-water intake individual

**Drinking Water – Artificial Sources**
- PHS recommends 0.7-1.2 mg/L (162 million people exposed)
  - 41% - 83% for average individual
  - 75% - 91% for high-water intake individual
Critical Health End Points

Enamel Fluorosis

Bone Fractures

Skeletal Fluorosis
Enamel Fluorosis

- Enamel fluorosis is a dose-related mottling of enamel ranging from mild discoloration to severe dark stains and pitting.

- Children (0-8 years) susceptible.

- Permanent condition.

- Historically, condition considered cosmetic because it is not associated with tooth loss, loss of tooth function, or psychological, behavioral, or social problems.
Committee considered moderate and severe forms separately.

Severe enamel fluorosis is associated with enamel loss and pitting.

Moderate enamel fluorosis is associated with mottling and staining of teeth, but no enamel loss or pitting.
Severe Enamel Fluorosis
Severe Enamel Fluorosis

Health Effect vs. Cosmetic Effect

Adverse health effect (10 of 12 members)

- Damage to the tooth; toxic effect consistent with prevailing risk assessment definitions of adverse health effects
- Treatment often considered
- Does it increase caries risk?
  - Plausible
  - Evidence suggestive but not conclusive
- Does it affect psychology, behavior, functioning?
  - Plausible, in children and parents
  - No studies specific to severe enamel fluorosis
Severe Enamel Fluorosis

Health Effect vs. Cosmetic Effect

Adverse dental/cosmetic effect (2 of 12 members)

- No new evidence suggests that severe enamel fluorosis, as experienced in the United States, affects a person’s ability to function.
- Enamel defects alone are not a sufficient basis to change the prevailing historical opinion that enamel fluorosis is a cosmetic effect.
- Should be prevented.
• Do the severest forms occur at 4 mg/L?
  - Yes
Severe Enamel Fluorosis in Children in the United States
Severe Enamel Fluorosis in Children in the United States

**Severe Enamel Fluorosis**

- Consensus that MCLG is not protective.

<table>
<thead>
<tr>
<th>Water fluoride</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>4 mg/L</td>
<td>~10%</td>
</tr>
<tr>
<td>&lt;2 mg/L</td>
<td>~0%</td>
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</table>
• Conclusion that the MCLG should protect against severe enamel fluorosis is consistent with recommendations of IOM.

• 25% to 50% of children exposed at 4 mg/L would be expected to consume more than the age-specific tolerable upper limits of fluoride.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Tolerable Upper Intake (IOM 1997)</th>
<th>Water Intake, mL/day (EPA 2004)</th>
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<tbody>
<tr>
<td></td>
<td>Fluoride, mg/day</td>
<td>50th Percentile</td>
</tr>
<tr>
<td>0-6 months</td>
<td>0.7</td>
<td>175</td>
</tr>
<tr>
<td>7-12 months</td>
<td>0.9</td>
<td>225</td>
</tr>
<tr>
<td>1-3 years</td>
<td>1.3</td>
<td>325</td>
</tr>
<tr>
<td>4-8 years</td>
<td>2.2</td>
<td>550</td>
</tr>
</tbody>
</table>
Moderate Enamel Fluorosis

- Characterization
  - Yellow to brown staining, no pitting

- From a cosmetic standpoint, moderate enamel fluorosis was found to occur in 4% to 15% of children at 2 mg/L. The prevalence of moderate cases classified as being of aesthetic concern (discoloration of the front teeth) is unknown.

- The degree to which moderate enamel fluorosis might go beyond a cosmetic effect to create an adverse psychological effect or an adverse effect on social functioning is not known.
Moderate Enamel Fluorosis

• SMCL does not completely prevent the occurrence of moderate enamel fluorosis.

• The available data indicate that fewer than 15% of children will experience moderate enamel fluorosis of aesthetic concern. This finding is consistent with EPA’s policy to reduce occurrence to 15% or less.
Bone Fracture

- Several new studies of fluoride and bone fracture
  - Populations exposed to fluoride at 2-4 mg/L in drinking water
  - Clinical trials of fluoride as a therapeutic agent

- Both types of studies indicate an increased risk of bone fracture. Bone concentrations of fluoride range from 5,400 to 12,000 mg/kg ash.

- Animal studies provide supporting evidence that although fluoride increases bone volume, there is less strength per unit volume. Bone strength begin to decline at bone concentrations of 6,000 to 7,000 mg/kg ash.
• Dose-response relationship is indicated.

• Biochemical and physiological data indicate a biologically plausible mechanism.

• The MCLG is likely not protective of bone fracture, particularly in some demographic subgroups prone to accumulate fluoride into their bones.
  - Three of 12 members concluded that the MCLG might not be protective of bone fracture. More evidence needed that bone fractures occur at an appreciable frequency in human populations exposed to fluoride at 4 mg/L before drawing a firm conclusion about fracture risk at the MCLG.
Skeletal Fluorosis

• Current basis of EPA’s MCLG is “crippling” skeletal fluorosis. Bone and joint condition characterized by an increase in bone density and the exacerbated growth of osteophytes in bones and joints. Arthritic-like pain, limitation of joint movement, muscle wasting, and deformities of the spine and joints.

• Since 1993: a few case reports, but no studies of incidence in U.S. populations exposed to fluoride at 4 mg/L. New pharmacokinetic estimates of bone accumulation of fluoride.

• Stage II skeletal fluorosis (stage before “crippling”) should be considered an adverse health effect. It is associated with sporadic pain, stiffening of joints, and of occasional osteophyte formation on articular joint surfaces.

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine
• Can bone fluoride concentrations associated with skeletal fluorosis be achieved from 70-year exposure to fluoride at 4 mg/L in drinking water?
  ▪ Compared pharmacokinetic model estimates with historical information on bone concentrations associated with different stages of skeletal fluorosis.
## Skeletal Fluorosis

<table>
<thead>
<tr>
<th>Skeletal Fluorosis Stage</th>
<th>Ash Concentration, ppm</th>
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<tbody>
<tr>
<td><strong>Normal Bone</strong></td>
<td>500-1,000</td>
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<tr>
<td><strong>Preclinical Stage</strong></td>
<td></td>
</tr>
<tr>
<td>asymptomatic, slight radiographically-detectable increases in bone mass</td>
<td>3,500-5,500</td>
</tr>
<tr>
<td><strong>Clinical Stage I</strong></td>
<td>6,000-7,000</td>
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<tr>
<td>Sporadic pain; stiffness of joints; osteosclerosis of pelvis &amp; vertebral column</td>
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<tr>
<td><strong>Clinical Stage II</strong></td>
<td>7,500-9,000</td>
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<tr>
<td>Chronic joint pain; arthritic symptoms; slight calcification of ligaments; increased osteosclerotic/cancellous bones; with/without osteoporosis of long bones</td>
<td></td>
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<tr>
<td><strong>Clinical Stage III: Crippling Fluorosis</strong></td>
<td>&gt; 8,400</td>
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<tr>
<td>Limitation of joint movement; calcification of ligaments/neck, vertebral column; crippling deformities/spine &amp; major joints; muscle wasting; neurological defects/compression of spinal cord.</td>
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Pharmacokinetic/regression models predict the following bone ash concentrations from 70 years of exposure to fluoride in drinking water: 10,000-12,000 ppm at 4 mg/L and 4,000-5,000 ppm at 2 mg/L.
- Pharmacokinetic models predict that bone concentrations associated with stage II skeletal fluorosis can be achieved from lifetime exposure to fluoride at 2 or 4 mg/L.

- No documented evidence that stage II skeletal fluorosis is occurring in U.S. populations. Stage III skeletal fluorosis appears to be a rare condition in the United States.

- More research is needed to determine whether the MCLG is protective of stage II skeletal fluorosis.
• Bone is the most biologically plausible site for cancer because fluoride is deposited into bone and has been shown to have mitogenic effects on bone cells in vitro.

• NTP study found a positive dose-response trend for osteosarcoma.

• Another animal study reported no increase in osteosarcoma in male rats, but the study had insufficient power to provide conflicting evidence for the trend.

• No new animal bioassays have been performed.
• Several new epidemiologic studies of the relation between fluoride and cancer. Results were mixed.

• Recent media attention has focused on an unpublished doctoral dissertation from the Harvard School of Public Health, which found an increase in osteosarcoma in young boys in a fluoridated community. Committee found the reported results to be consistent with some previous studies, but found it had methodological weaknesses and was inadequately documented on some points.
The committee concluded that the data are tentative and mixed regarding the potential for fluoride to cause cancer, particularly of the bone.

A hospital-based case-control study of osteosarcoma and fluoride is currently underway. Study should help identify future research that would be useful for studying fluoride’s carcinogenic potential.
Recommendations

- New risk assessment should be performed on fluoride. The assessment should include new data on health risks, better estimate of total exposure to fluoride, and updated approaches to risk assessment. Key end points for the risk assessment are severe enamel fluorosis, bone fracture, and stage II skeletal fluorosis.

- Committee’s conclusions about the adverse effects at the MCLG and SMCL do not address the lower concentrations of exposure that occur with water fluoridation.