Fluoridation as a Case Study in Hormesis

Dennis E. Jones
Christopher T. De Rosa
Carolyn Tylenda

Agency for Toxic Substances and Disease Registry
ATSDR Mission

* To prevent or mitigate adverse human health effects and diminished quality of life resulting from exposure to hazardous substances in the environment.

* (Federal Register 54:33617, 1989)
ATSDR Activities

- Health Assessments
- Health Consultations
- Emergency Response
- Health Studies
- Disease Registries
- Health Education
- Toxicological Profiles
ATSDR Toxicological Profiles

- Provide Comprehensive Data Review
- Identify Data Gaps
- Identify Research Needs
- Develop MRLs
ATSDR Minimal Risk Level (MRL)

An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure.
Formula for MRL/RfD

MRL (or RfD) = \frac{\text{NOAEL/LOAEL/BMD}}{\text{UF}}

- NOAEL: no observed adverse effect level
- LOAEL: lowest observed adverse effect level
- BMD: benchmark dose (equivalent to a NOAEL)
- UF: uncertainty factor
Example BMD Curve
Hometic Response

TYPICAL DOSE RESPONSE

RESPONSE

EXPOSURE

0 20 40 60

0 1

-1
**ATSDR Working Definition: Hormesis**

* ...hormesis (i.e., the induction of beneficial effects by low doses of otherwise harmful physical or chemical agents)...

* De Rosa et al., 1998
ATSDR MRLs and Hormesis

- Zn
- Cr
- Mn
- Se
- Co
- Cu
Chromium Health Guidance Value
(Chronic Oral)

• NOAEL/LOAEL: Insufficient Data

• ESADDI: 50-200 µg/day

• Provisional Guidance: 0.003 mg/kg/day
Manganese Health Guidance Value (Chronic Oral)

- **NOAEL/LOAEL:** Insufficient Data
- **ESADDI:** 2-5 mg/day
- **Provisional Guidance:** 0.07 mg/kg/day
Fluoride Chemical Information

- Ionic form (e.g., salts) of Fluorine (F)
- Smallest Halogen
- Most Electronegative Element
- Most Reactive Element
- Substitutes for –OH in Hydroxyapatite
- Affects Bone and Tooth Enamel
Dental Health and Fluoride

Decay (deficient fluoride)
Healthy Teeth (optimal fluoride)
Fluorosis (excess fluoride)
Fluoride Effect on Caries and Dental Fluorosis (Dean, 1942)
# Fluoride Drinking Water Recommendations

<table>
<thead>
<tr>
<th>Optimal Level</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ppm</td>
<td>Dean, 1942</td>
</tr>
<tr>
<td>0.7 – 1.2 ppm</td>
<td>DHHS, 2000</td>
</tr>
</tbody>
</table>
Health Risk of Dental Fluorosis

*...the cosmetic risk of mild enamel (dental) fluorosis...

*ADA, 2006

**...all forms of enamel fluorosis, including the severest form, have been judged to be aesthetically displeasing but not adverse to health.

**NRC, 2006
Fluoride Effect on Caries and Dental Fluorosis (Dean, 1942)
Fluoride and Bone Effects

* As with the dental effects, fluoride has both beneficial and adverse effects on bone.

* ATSDR, 2003
## Fluoride Effect

### Bone Mineral Density

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sowers et al., 1991</td>
<td>no effect</td>
</tr>
<tr>
<td>Kroger et al., 1994</td>
<td>increase</td>
</tr>
<tr>
<td>Cauley et al., 1995</td>
<td>no effect</td>
</tr>
<tr>
<td>Phipps et al., 1998</td>
<td>decrease, increase</td>
</tr>
<tr>
<td>Lehmann et al., 1998</td>
<td>no effect</td>
</tr>
<tr>
<td>Phipps et al., 2000</td>
<td>increase</td>
</tr>
<tr>
<td>Study</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Madans et al., 1983</td>
<td>no effect</td>
</tr>
<tr>
<td>Simonen et al., 1985</td>
<td>decrease</td>
</tr>
<tr>
<td>Arnala et al., 1986</td>
<td>no effect</td>
</tr>
<tr>
<td>Jacobsen et al., 1990</td>
<td>increase</td>
</tr>
<tr>
<td>Cooper et al., 1990</td>
<td>no effect</td>
</tr>
<tr>
<td>Danielson et al., 1992</td>
<td>no effect</td>
</tr>
<tr>
<td>Jacobsen et al., 1993</td>
<td>decrease</td>
</tr>
<tr>
<td>Karagas et al., 1996</td>
<td>increase</td>
</tr>
</tbody>
</table>
“Effect of Long-Term Exposure to Fluoride in Drinking Water on Risks of Bone Fractures” (Li et al.; 2001)

• **QUESTION:**
  - “whether the exposure to fluoride in drinking water for cariostatic purposes increases the risk of fractures”

• **PURPOSE:**
  - “determine the prevalence of bone fractures in Chinese populations residing in rural communities of various fluoride concentrations in drinking water”
“Effect of Long-Term Exposure to Fluoride in Drinking Water on Risks of Bone Fractures”
(Li et al. ; 2001)

- 8266 Chinese Subjects
- Male/Female/Rural
- ≥ 50 Years of Age
- ≥ 25 Years Continuous Residence
- Six Fluoride Drinking Water Levels
Effect of Long-Term Exposure to Fluoride in Drinking Water on Risks of Bone Fractures;” (continued) 
(Li et al. ; 2001)

• Gender, Smoking, Diet, Alcohol, Physical Activity, BMI, Ca, Al, Pb, Cd, Fe, Zn, As

• Drinking Water and Diet - Only Exposure Sources

• Bone Fracture Prevalence
## Fluoride in Drinking Water

**Li et al. (2001) Study**

<table>
<thead>
<tr>
<th>Group</th>
<th>Fluoride (ppm)</th>
<th>n</th>
<th>Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25 – 0.34</td>
<td>1363</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>0.58 – 0.73</td>
<td>1407</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td>1.00 – 1.06</td>
<td>1370</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>1.45 – 2.19</td>
<td>1574</td>
<td>7.0</td>
</tr>
<tr>
<td>5</td>
<td>2.62 – 3.56</td>
<td>1051</td>
<td>8.0</td>
</tr>
<tr>
<td>6</td>
<td>4.32 – 7.97</td>
<td>1501</td>
<td>14.0</td>
</tr>
</tbody>
</table>
Bone Fracture Prevalence
Li et al. (2001) Study

- Hip Fractures - Since of 20 Years of Age
- Bone Fractures - Since 50 Years of Age
- Bone Fractures - Since 20 Years of Age
Hip Fracture Prevalence Since the Age of 20 Years
Li et al. (2001) Study

- Slight Increase Above 1.00 – 1.06 ppm
- No Significant Difference at any Fluoride Exposure Level
- Number of Hip Fractures…
  “Relatively Small”
Bone Fractures Since 50 Years of Age

Li et al. (2001) Study

Fluoride Drinking Water Concentration (ppm):
- .25-.34
- .58-.73
- 1.00-1.06
- 1.45-2.19
- 2.62-3.56
- 4.32-7.97

Bone Fracture Prevalence (%):
- 2.58-.73
- 1.00-1.06
- 1.45-2.19
- 2.62-3.56
- 4.32-7.97

ATSDR
Bone Fractures Since 20 Years of Age
Li et al. (2001) Study

Fluoride Drinking Water Concentration (ppm)

Bone Fracture Prevalence (%)

* p<0.05 as compared to the group of 1.00-1.06
## Fluoride MRL Derivation

<table>
<thead>
<tr>
<th>Comparison Group</th>
<th>Fluoride Concentration (ppm)</th>
<th>Fluoride Dose (mg/kg/day)</th>
</tr>
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<tbody>
<tr>
<td>NOAEL</td>
<td>1.00 – 1.06</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>2.62 – 3.56</td>
<td>0.15</td>
</tr>
</tbody>
</table>

UF (uncertainty factor) = 3

\[
\text{MRL} = \frac{\text{NOAEL}}{\text{UF}} = 0.05 \text{ mg/kg/day}
\]
Bone Fracture Since 20 Years of Age
Li et al. (2001) Study

Fluoride Drinking Water Concentration (ppm)

Bone Fracture Prevalence (%)

*p < 0.05 as compared to the group of 1.00-1.06

0.25-0.34
0.58-0.73
1.00-1.06
1.45-2.19
2.62-3.56
4.32-7.97

7.41*
6.40
5.11
6.04
6.09
7.40 *
Fluoride Health Guidance Values Comparison

- MRL = 0.05 mg/kg/day
- MRL Equivalent\(_{(DW)}\) = 1.75 ppm = 1.75 mg/L
- MCL = 4 mg/L
- MCLG = 4 mg/L
- SMCL = 2 mg/L
Summary

Fluoride in Drinking Water

- Hormetic Effect – Dental Health (1 ppm)
- Hormetic Effect – Bone (1 ppm)
- Hormetic Dose - MRL Comparison Value (1 ppm)
- Only Chemical
  - 2 Hormetic Effects
  - 1 ppm Optimal Dose for Each Effect
  - Bases for 2 HGVs
Thank You
# Bone Fractures Since Age 50 & Fluoride

Li et al. (2001)

<table>
<thead>
<tr>
<th>Group</th>
<th>Fluoride (ppm)</th>
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