Fluoridation as a Case Study in Hormesis

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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)**

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ATSDR Activities

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

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ATSDR Toxicological Profiles

- **Provide Comprehensive Data Review**
- **Identify Data Gaps**
- **Identify Research Needs**
- **Develop MRLs**

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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.

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Formula for MRL/RfD

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

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

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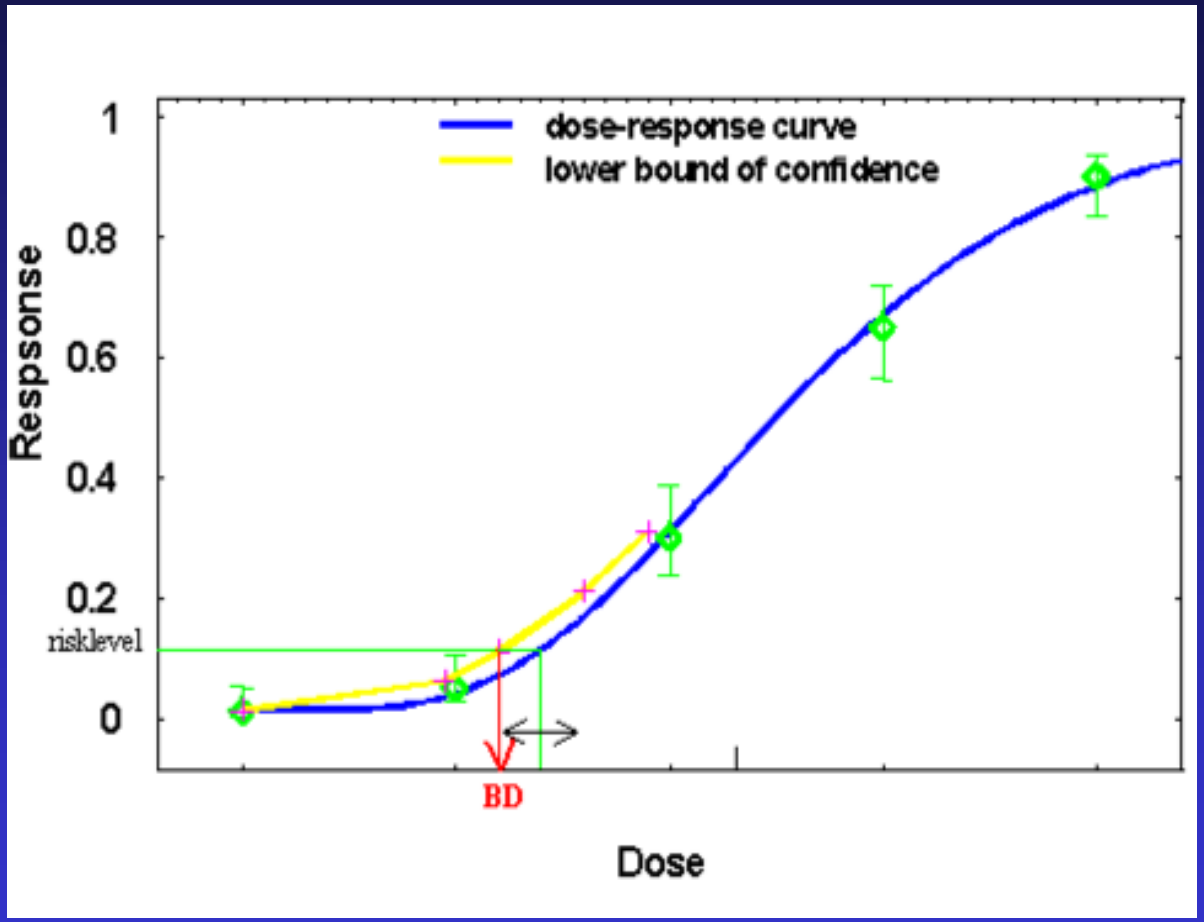
Example BMD Curve



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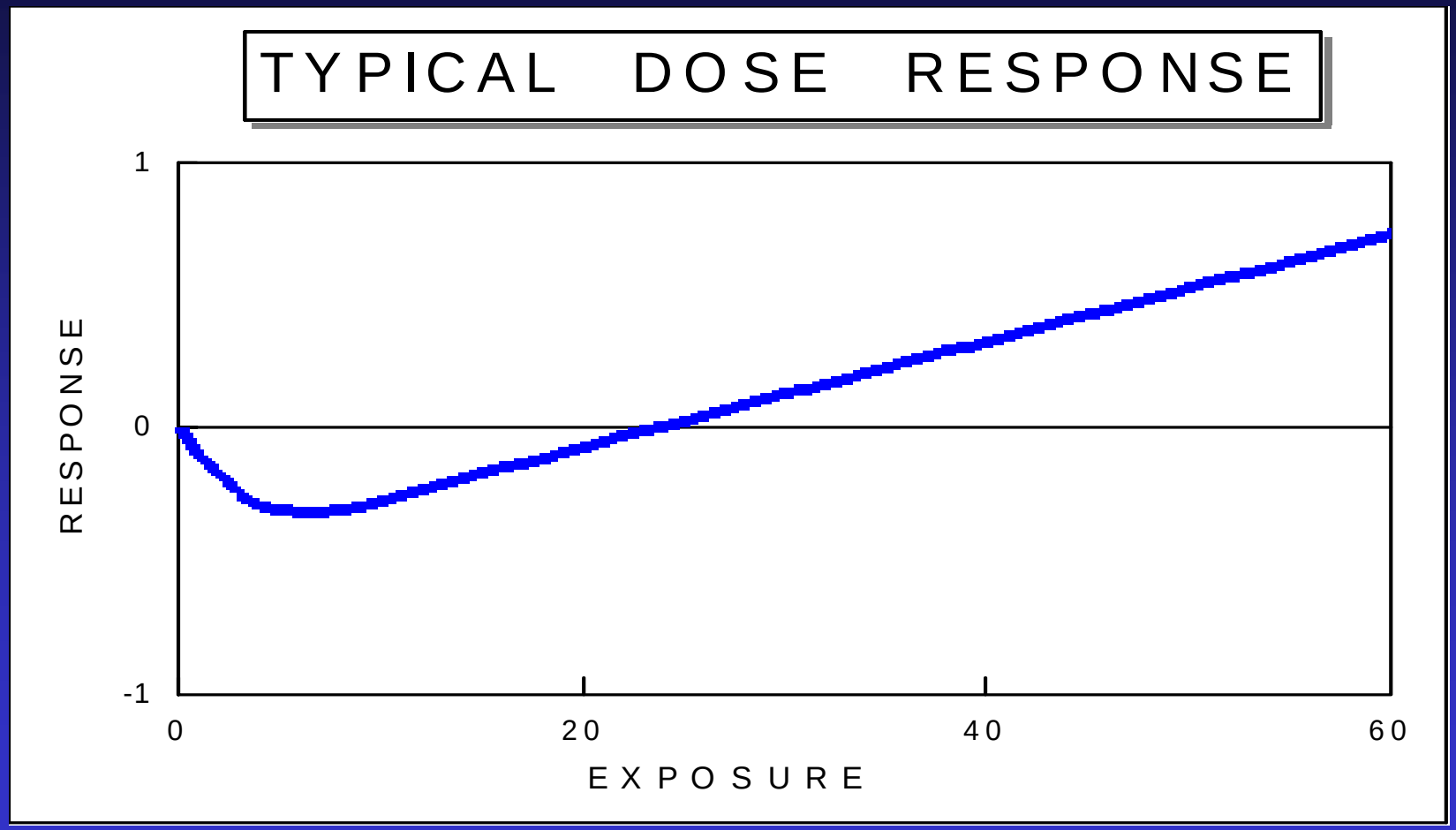
Hometic Response



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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

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ATSDR MRLs and Hormesis

- Zn
- Cr
- Mn
- Se
- Co
- Cu

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Chromium Health Guidance Value (Chronic Oral)

- **NOAEL/LOAEL: Insufficient Data**
- **ESADDI: 50-200 µg/day**
- **Provisional Guidance: 0.003 mg/kg/day**

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Manganese Health Guidance Value (Chronic Oral)

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

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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

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Dental Health and Fluoride

Decay
(deficient fluoride)

Healthy Teeth
(optimal fluoride)

Fluorosis
(excess fluoride)

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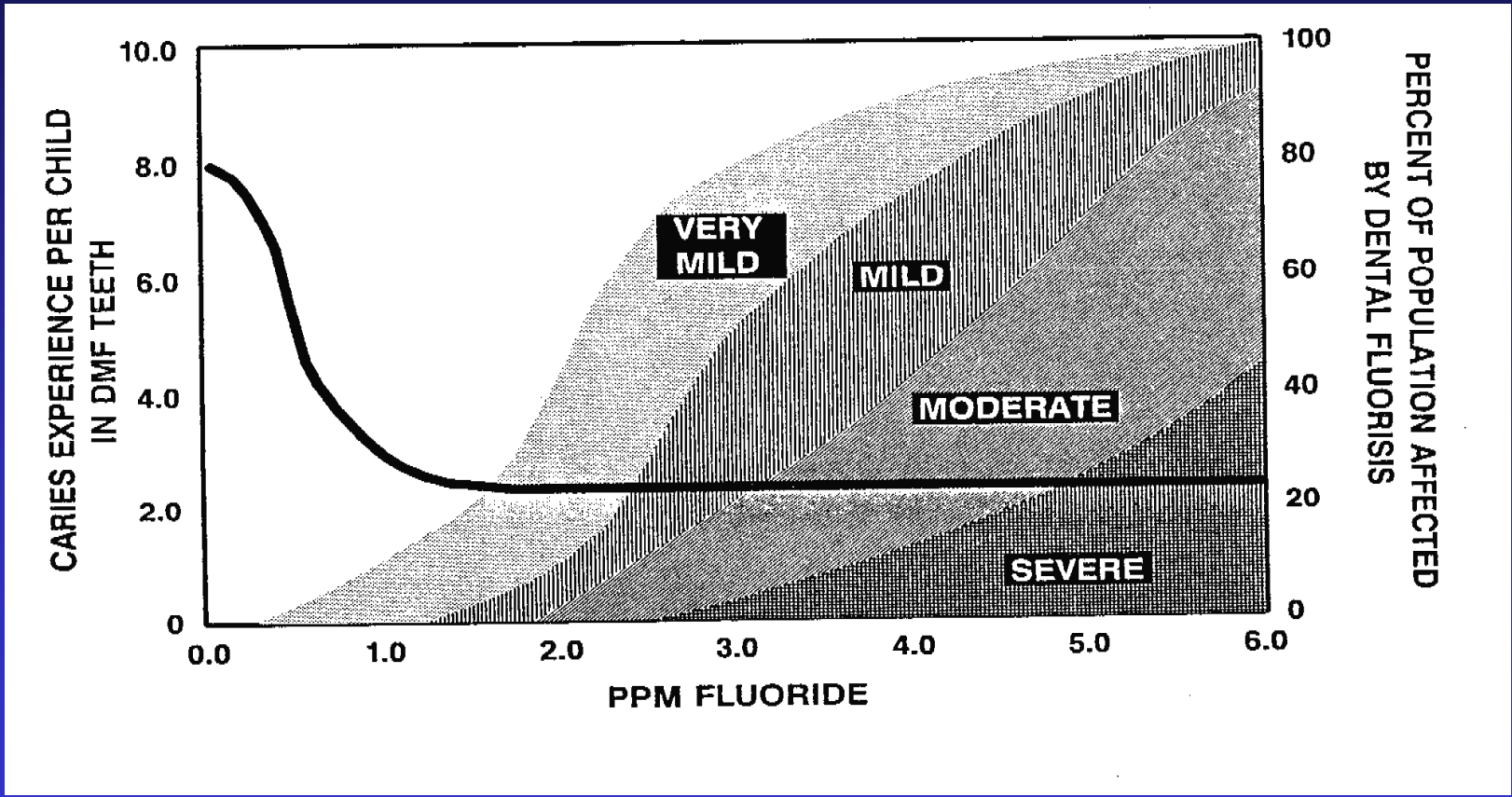
Fluoride Effect on Caries and Dental Fluorosis (Dean, 1942)



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Fluoride Drinking Water Recommendations

Optimal Level	Reference
1 ppm	Dean, 1942
0.7 – 1.2 ppm	DHHS, 2000

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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

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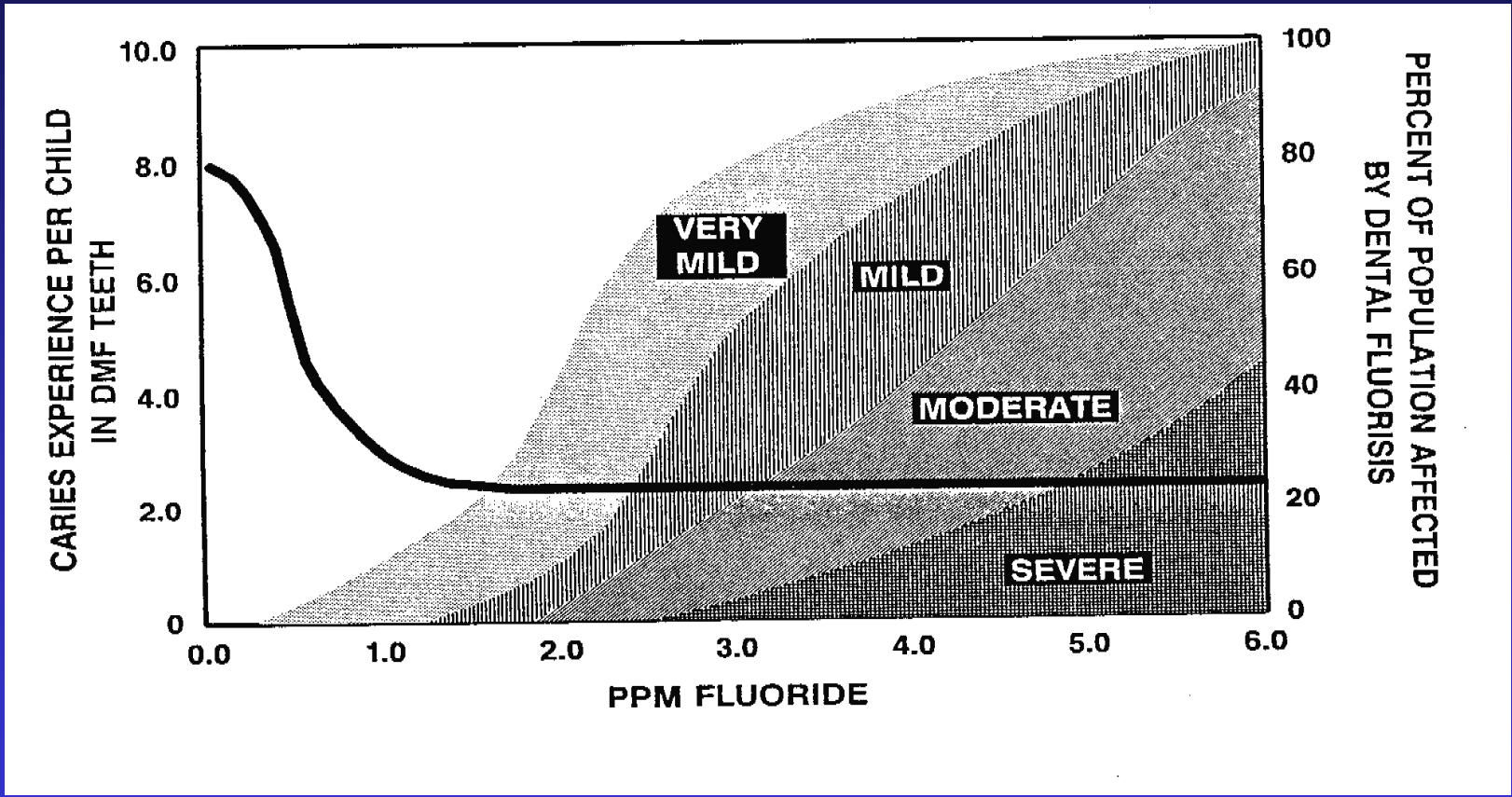
Fluoride Effect on Caries and Dental Fluorosis (Dean, 1942)



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Fluoride and Bone Effects

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

* ATSDR, 2003

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Fluoride Effect
Bone Mineral Density

Study	Results
Sowers et al., 1991	no effect
Kroger et al., 1994	increase
Cauley et al., 1995	no effect
Phipps et al., 1998	decrease, increase
Lehmann et al., 1998	no effect
Phipps et al., 2000	increase

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Flouride Effect
Bone Fracture Risk

Study	Results
Madans et al., 1983	no effect
Simonen et al., 1985	decrease
Arnala et al., 1986	no effect
Jacobsen et al., 1990	increase
Cooper et al., 1990	no effect
Danielson et al., 1992	no effect
Jacobsen et al., 1993	decrease
Karagas et al., 1996	increase

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"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"**

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"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**

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"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**

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Fluoride in Drinking Water
Li et al. (2001) Study

Group	Fluoride (ppm)	n	Dose (mg/day)
1	0.25 – 0.34	1363	0.7
2	0.58 – 0.73	1407	2.0
3	1.00 – 1.06	1370	3.0
4	1.45 – 2.19	1574	7.0
5	2.62 – 3.56	1051	8.0
6	4.32 – 7.97	1501	14.0

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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**

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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"

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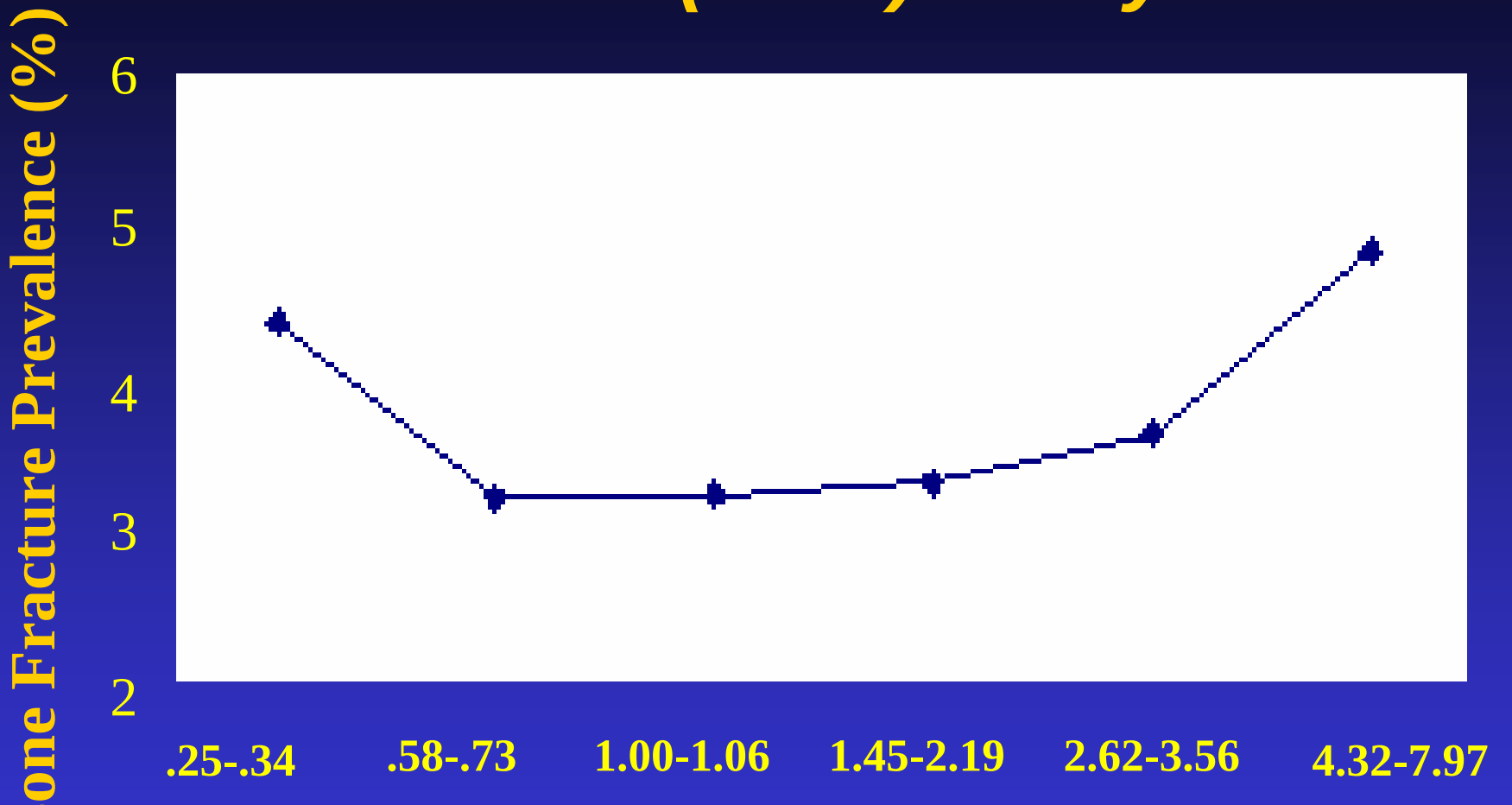
Bone Fractures Since 50 Years of Age
Li et al. (2001) Study



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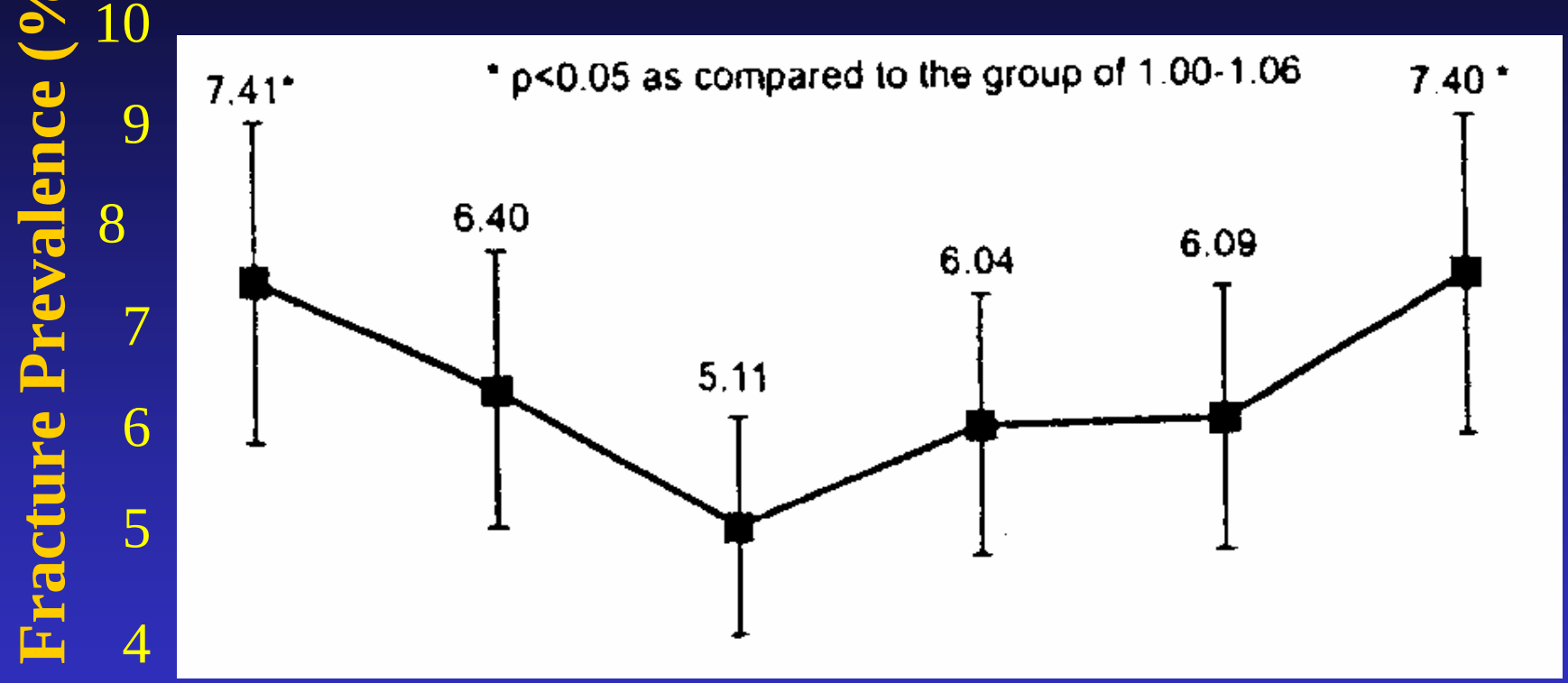
Bone Fractures Since 20 Years of Age
Li et al. (2001) Study



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Fluoride MRL Derivation

	Fluoride Conc. (ppm)	Fluoride Dose (mg/kg/day)
Comparison Group	1.00 – 1.06	0.05
NOAEL	2.62 – 3.56	0.15

UF (uncertainty factor) = 3

$$\text{MRL} = \frac{\text{NOAEL}}{\text{UF}} = 0.05 \text{ mg/kg/day}$$

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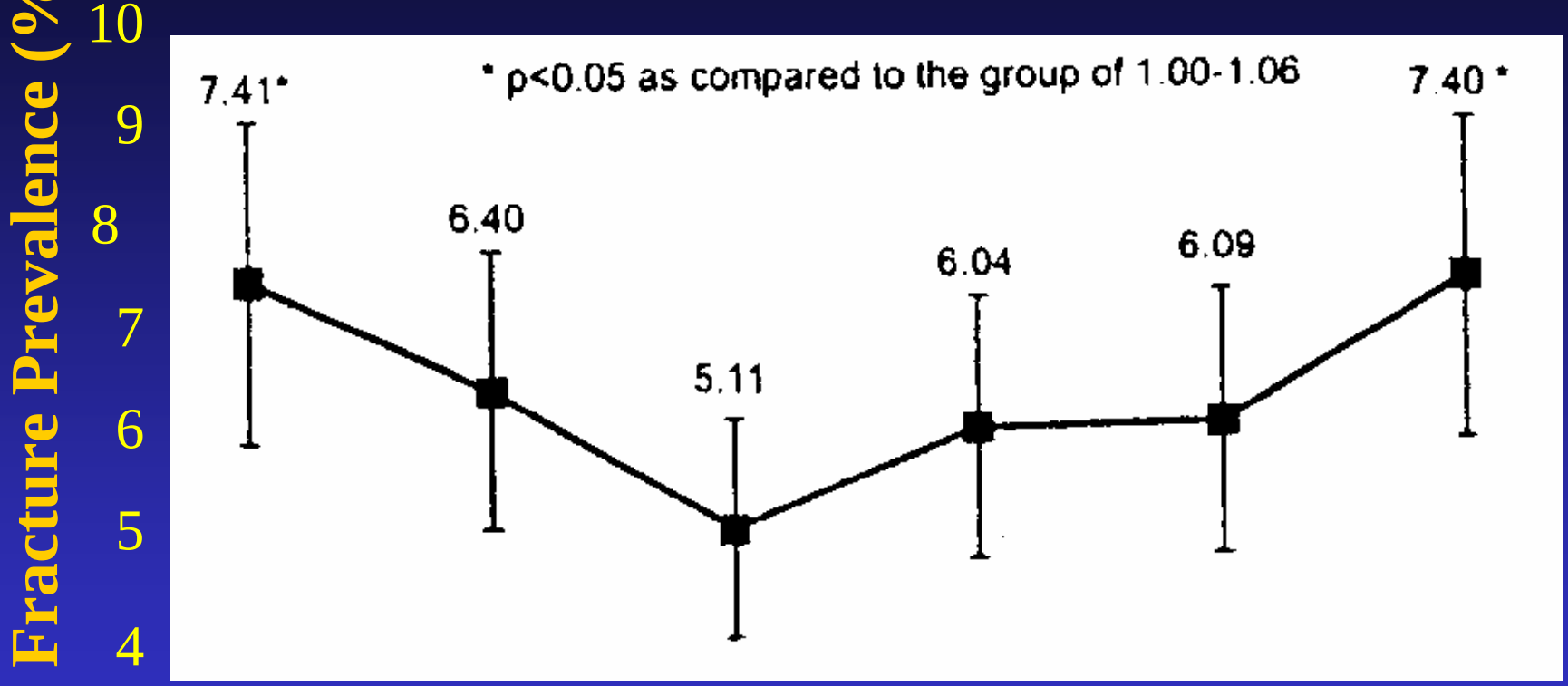
Bone Fracture Since 20 Years of Age
Li et al. (2001) Study



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Fluoride Health Guidance Values Comparison

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

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Summary
Fluoride in Drinking Water

- Hormetic Effect – Dental Health (1 ppm)
- Hormetic Effect – Bone (1 ppm)
- Hormetic Dose - MRL Comparison Value (1ppm)
- Only Chemical
  - 2 Hormetic Effects
  - 1 ppm Optimal Dose for Each Effect
  - Bases for 2 HGVs

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Thank You

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Bone Factures Since Age 50 & Fluoride
Li et al. (2001)

Group	Fluoride (ppm)	n	Fracture %
1	0.25 – 0.34	1363	4.33
2	0.58 – 0.73	1407	3.20
3	1.00 – 1.06	1370	3.28
4	1.45 – 2.19	1574	3.38
5	2.62 – 3.56	1051	3.62
6	4.32 – 7.97	1501	4.80

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