Chronically Underestimated:

The impact of high early life water intake rates and short-term effects for deriving health-protective drinking water criteria

US EPA Temporal Exposures Workshop
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Outline

- **Background**

- **Evolving of Policy & Science**

- **Revised Methods – Multiple Durations**

- **Results**

- **Challenges**

- **Conclusions**

Background

- **Health-based drinking water guidance (HBG)**

" . . . a concentration of a contaminant, or mixture of contaminants, that is likely to pose little or no risk to human health"

Regardless of life-stage OR Duration

Background cont.

- **Basic equation from EPA**
  - Health endpoints other than cancer
  - Reference dose (RfD) represents a no effect dose
  - Focus - Chronic effect from chronic exposure
- **Used for drinking water health based guidance (HBG)** (MDH pre-2008)

$$\text{HBG } (\mu g/L)_{chronic} = \frac{RfD_{chronic} \times 1000 \text{ ug/mg} \times RSC}{\text{Intake Rate}_{adult/chronic}}$$

- **Assumption: lower chronic reference dose and long term exposure offers maximum protection**

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Evolving Policy & Science

Consideration of infants & children in setting standards
[NAS 1993 report: Pesticides in the Diets of Infants and Children]

- **Federal Level**
  - Food Quality Protection Act 1996
  - Amendments to Safe Drinking Water Act
  - 1996 EPA Science Policy Council
  - 1996 Executive Order by President Clinton

- **State Level**
  - 2001 Health Standards Statute (air & water)

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Evolving Policy & Science

- A Review of the Reference Dose and Reference Concentration Process (EPA 2002)

    - Additional testing on life stage differences

    - Reference values for acute, short-term, subchronic & chronic

- Estimated Per Capita Water Ingestion and Body Weight in the United States – An Update (EPA 2004)

- A Framework for Assessing Health Risks of Environmental Exposures to Children (EPA 2006)

- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (2005)

    - Lifetime cancer slope factors

    - Age-Dependent Adjustment Factors (ADAFs)

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Need for Revised Methods?

Standard Noncancer Equation (pre-2008)

$$\text{HBG (µg/L)}_{chronic} = \frac{RfD_{chronic} \text{ x 1000 ug/mg } \text{ x RSC}}{\text{Intake Rate}_{adult/chronic}}$$

Toxicity

• Protective of sensitive life stages?

• Protective of < chronic durations?

Exposure

• Protective of high short-term exposures?

• Update Water Intake Rates

GOAL

- **To derive health-based drinking water criteria that adequately protects susceptible life-stages and highly exposed populations**

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Revised Methods

Durations (EPA 2002)

- Acute: $\leq$ 24 hours

- Short-term: > 24 hours - up to 30 days

- Subchronic: > 30 days, up to ~10% of a lifespan (~90 days in typical laboratory rodent studies)

- Chronic: > ~ 10% of a life span

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Revised Methods

For Each Duration (if sufficient data was available)

- **Toxicity Assessment (RfD derivation)**
    - Consider timing (e.g., life stage) & duration of dosing
    - Consider entire database in identifying 'co-critical' effects
    - Consider entire database in selecting type & magnitude of UFs

- **Exposure Assessment (water intake rate)**
    - Consider life-stage in calculating corresponding duration intake rates
    - Use updated age specific intake rate data

- **Relative Source Contribution (RSC)**
    - Based on "Exposure Decision Tree for RfD Apportionment" (EPA 2000)

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Revised Methods

Standard Noncancer Equation

$$\text{HBG (µg/L)}_{duration} = \frac{\text{RfD}_{duration} \times 1000 \text{ ug/mg} \times \text{RSC}_{duration}}{\text{Intake Rate}_{duration}}$$

Where:

HBG (µg/L) = Health-based Guidance value for a given duration

RfD (mg/kg-day) = Reference Dose for a given duration (acute, short-term, subchronic, and chronic)

Intake Rate (L/kg-day) = Water intake rate corresponding to given duration

RSC = Relative Source Contribution, varies by duration and age group

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Results

73 chemical assessments completed

- Solvents, pesticides, consumer product/personal care related chemicals, pharmaceuticals, . . .

- Short-term, subchronic and chronic values derived for 53 (~73%)

  - Remaining 20 chemicals had only subchronic & chronic (15) or only chronic value (5)

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Results - Toxicity

Reference Doses

- Decreased with increasing duration
  - Short-term > Subchronic > Chronic
  - Chronic RfD was lowest for more than 90 percent (48/53)

- Exceptions - Shorter Duration RfD was lowest
  - Developmental toxicants
  - Cholinesterase inhibitors

- MDH set the final Chronic RfD to lowest RfD value
  (EPA 2002)

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Results - Toxicity

Comparison	Number of Chemicals	Geometric Mean ± GSD	90th percentile	95th percentile
Short-term RfD to Chronic RfD Ratio				
	53[a]	3.7 ± 3.0	19.1	24.9
	16[b]	2.8 ± 2.1	5.6	9.1
Subchronic RfD to Chronic RfD Ratio				
	53[a]	2.0 ± 2.1	4.4	10.0
	16[b]	1.6 ± 1.9	4.2	4.6

[a] Includes chronic RfDs based on less than chronic studies
[b] Limited to assessments in which comparison is across laboratory animal studies and chronic RfD is based on chronic study.

Results - Toxicity

Comparison	No. of Chemicals	Geometric Mean ± GSD	95th percentile
Short-term NOAEL to Chronic NOAEL Ratio			
Batke et al 2011	14	3.4 ± 3.7	29.2
Zarn et al 2011 (pesticides)	Rat 107 Mouse 56	4.3 ± 4.7 3.4 ± 3.6	53.2 23.7
Groeneveld et al 2004	35	4.9 ± 3.5	38.6
Kramer et al 1996	71	4.1 ± 4.4	46
Subchronic NOAEL to Chronic NOAEL Ratio			
Batke et al 2011	58	1.4 ± 2.1	4.7
Zarn et al 2011 (pesticides)	Rat 222 Mouse 99	2.5 ± 3.4 2.2 ± 3.9	17.4 21.4
Bokkers and Slob 2005	68	1.5 ± 5.3	22.7
Groeneveld et al 2004	70	2.3 ± 3.6	18.4
Pieters et al 1998	149	1.7 ± 5.6	29

Results – Exposure

Age-Specific Water Intake Rates (EPA 2004)
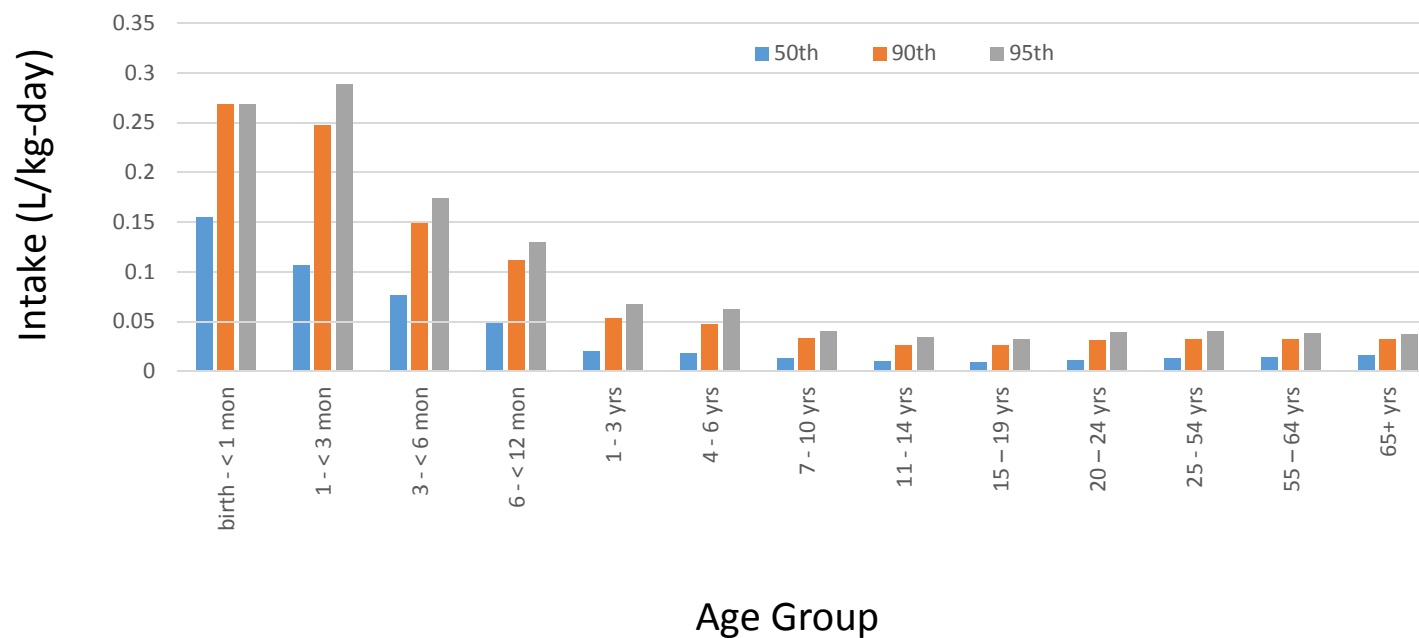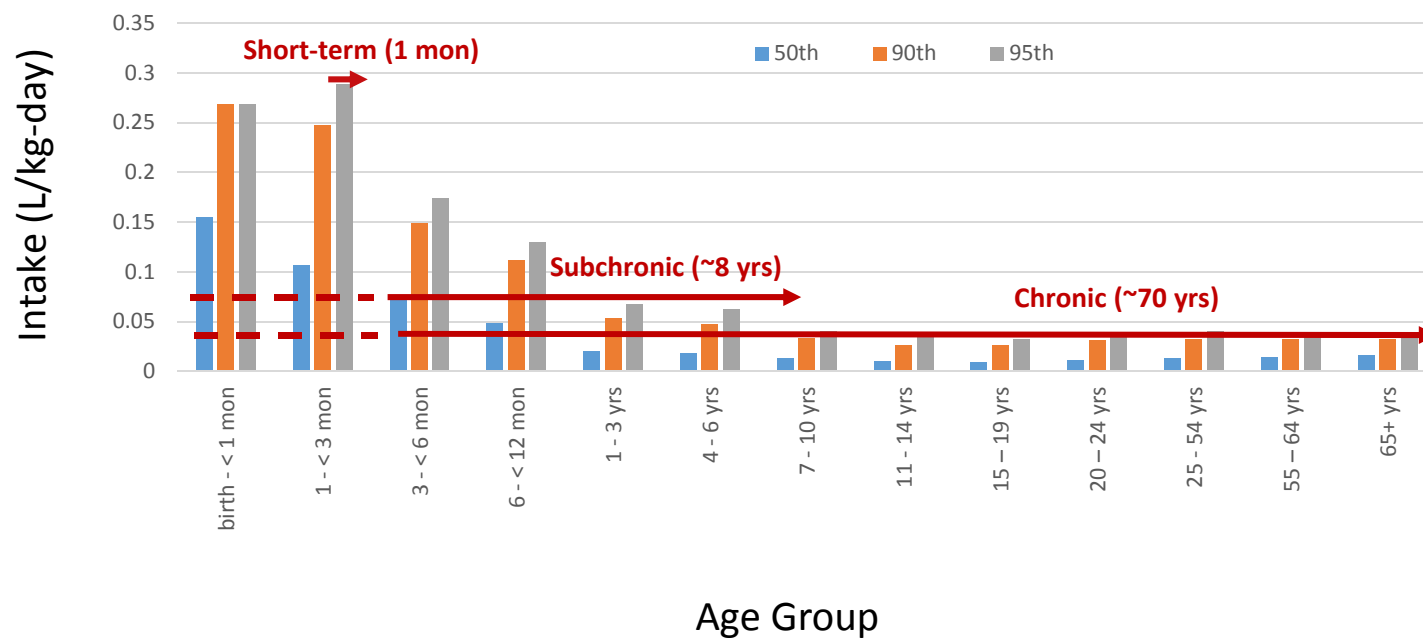
Results - Exposure

Water Intake Rate (L/kg per day)

- Decreased with age* (short-term > subchronic > chronic)

- Infant intake rates much higher than adults (mean values ~10-fold higher; 90th & 95th percentiles ~7-fold higher)

- By ~7 yrs of age similar to adult intake rates

- Calculated time-weighted average over exposure duration

*Not unique to drinking water – skin surface area as well as food, soil, and air intakes higher in early life

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Results – Exposure

Default* Duration Specific Water Intake Rates

*default value – different life-stage or duration used if chemical specific information available

Results – Exposure

Relative Source Contribution Factor (EPA 2000)

- Used to account for exposures other than ingestion of drinking water (e.g., dermal & inhalation from water use; food; soil/dust; consumer products; etc.)

- Chemical-specific or Default (range 0.2 to 0.8)

- Changes with age and exposure patterns

- Young infants have more limited exposures

- Older infants, toddlers, children and adults have more varied exposures

Result - higher RSC for infants [Exceptions - highly volatile chemicals or baby consumer products]

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Results – HBGs

Standard Noncancer Equation

$$\text{HBG (µg/L)}_{duration} = \frac{\text{RfD}_{duration} \ \text{x 1000 ug/mg} \ \text{x} \ \text{RSC}_{duration}}{\text{Intake Rate}_{duration}}$$

Where:

HBG (µg/L) = Health-based Guidance value for a given duration

RfD (mg/kg-day) = Reference Dose for a given duration

Intake Rate (L/kg-day) = Water intake rate corresponding to given duration
- *Default: Acute/Short-term (1 – 3 month infant); Subchronic (TWA birth to 8 yrs); and Chronic (TWA birth to 70 yrs)*

RSC = Relative Source Contribution
- *Default: Acute/Short-term – 0.5 [except: highly volatile chemicals & baby consumer product (0.2) and prescription drugs (0.8)]; Subchronic and Chronic - 0.2 [except prescription drugs (0.8)]*

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Results – HBGs

Health-based Guidance (HBG)

- Unlike RfDs, HBGs **did not** decreased with increasing duration

- Chronic duration HBGs were lower than shorter duration for 28 of the 53 chemicals (~53%)

- The 7-fold difference in short-term intake rate 'overwhelmed' the 2-4 fold differences in RfDs

- MDH set the final Chronic HBG to the lowest HBG value

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Challenges

- **Toxicity data limitations**
  - Lower quality of shorter duration studies
  - Inadequate reporting of effects at interim time points
  - Latent effects of early-life exposures

- **Exposure data limitations**
  - Early-life exposures
    - Often only have measure of maternal exposure in laboratory animal studies
  - Cumulative exposures to inform RSC, especially for high short-term exposures

- **Resources**
  - Time intensive – resulting in fewer chemicals assessed

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Conclusions

- **Results support recommendations of EPA 2002 report** (i.e., calculation of multiple duration RfDs)

- **Results demonstrate importance** (necessity?) **of evaluating shorter durations to ensure protectiveness**

- **In absence of shorter duration RfDs - use chronic RfD may be reasonable option for screening level assessment** (option suggested by EPA 2002)

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Questions?

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Methodology can be found at:
http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf

Health-based Guidance values can be found at:
http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html