ORIGINAL: 2547

A Fresh Look at the Uncertainty Factor Adjustment in the Methylmercury RfD

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RfD Derivation 101 – UFs

- $$RfD = \frac{\text{NOAEL (or LOAEL, or BMDL)}}{(UF_1 \times UF_2 \ldots UF_i)}$$

- UF = **Uncertainty** Factor
  - this is **NOT a "safety" factor**
    - not designed to add an extra margin of safety
  - intended to account for uncertainties in the NOAEL/BMDL derivation that, if known, could results in a smaller NOAEL/BMDL

NOAEL- No Observed Adverse Effect Level

LOAEL- Lowest Observed Adverse Eff Level

Bench-Mark Dose Lower Boundy

RfD Derivation 101 – UFs – cont'd

- Uncertainty Factor categories
  - UF_A - animal → human
  - UF_L - LOAEL → NOAEL
  - UF_{SC} - subchronic → chronic
  - **UF_H - average humans → sensitive humans**
  - **UF_D - database insufficiency**
  - (UF_M – modifying factor)

RfD Derivation 101 – UFs – cont'd

- UFs generally applied as factor of 3 or 10
  - 1 or ½ log unit
- However, there is no formal requirement restricting the UF to these values

The Current RfD

- UF = 10

- There are at least two new developments that could affect the appropriate value of the UF
  - cord blood:maternal blood Hg ratio
    - 1.7 (Stern and Smith, 2003)
  - re-analysis of the maternal dose corresponding to the cord blood BMDL (" the dose conversion")
    - (Stern, 2005)
    - incorporates cord:maternal ratio

The Current RfD cont'd

- Ideally, we would insert the new information into the existing UF structure
- Unfortunately, the structure of the current UF derivation is unclear and ambiguous

The Current RfD cont'd

- Three sources of information about the structure of the current UF adjustment
  - IRIS entry
  - Rice et al. (2003)
    - Methods and rationale for derivation of a reference dose for methylmercury by the U.S. EPA.
  - Rice (2004)
    - The U.S.EPA reference dose for methylmercury: sources of uncertainty

IRIS
INTEGRATE
RISK
INFO
SYSTEM

The Current RfD UF issues – cont'd

- These sources do not agree as to how and whether the cord blood:maternal blood Hg ratio was addressed in the UF for toxicokinetics

- If the dose conversion is now adjusted from a 1.0 cord:maternal ratio to a 1.7 ratio, would the UF of 3 for toxicokinetics need to be reduced to avoid double counting?
  - if so, by how much?

- There is now clarity as to the cord:maternal ratio
  - It is no longer necessary to treat is as an uncertainty

The Current RfD Issues – cont'd

- **UF_H (sensitive humans)**
  - IRIS
    - "A quantitative uncertainty analysis of toxicodynamics was not possible. However, the population of the Faroe Islands is ... extremely homogeneous. The average toxicodynamic response of this population compared with that of the United States ... is unknown. .. A threefold UF for toxicodynamic variability and uncertainty was applied"

The Current RfD–UF issues–cont'd

- UF_D (database uncertainty)
  - EPA allocated the entire UF of 10 to toxicokinetics (i.e., variability in the dose conversion, with or without cord:maternal ratio), and toxicodynamics (i.e., sensitive humans),
  - it is clear that uncertainty about whether **other endpoints** might be more sensitive than neurodevelopment is **not addressed in the UF**
    - **cardiovascular**
    - **sequalae with ageing**
    - **immunotoxicity**

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A Modest Proposal .

- It would be informative to examine what the UF might look like if we apply the new information and new perspectives in a new UF derivation
  - Dose conversion with updated cord:maternal ratio
  - cardiovascular effect data
  - fresh look at sensitive populations

The Dose Conversion

- The dose conversion is derived probabilistically (Monte Carlo)
  - **captures the population variability in the maternal dose corresponding to the cord blood BMDL**
- In the NAS/NRC assessment and in EPA's RfD derivation, there was uncertainty about appropriate central tendency estimates in the analysis
  - **central tendency and variability were separated**
  - **mean maternal dose was estimated**
  - **variability was incorporated as a UF**
    - **the variability is the UF of 3 for "toxicokinetic variability"**

The Dose Conversion – cont'd

- Recent re-analysis (Stern, 2005) of the dose conversion is a more careful analysis.
  - largely uses maternal physiological parameters specific to pregnancy .
  - issues of central tendency largely eliminated
- No longer useful to separate central tendency and variability estimates
  - can select the appropriate percentile of the distribution of maternal dose corresponding to the BMDL
    - e.g., 58 ug/L

The Dose Conversion – cont'd

- **Updated cord:maternal ratio (1.7) and its variability (Stern and Smith 2003) are incorporated directly**

- Estimated maternal dose for a cord blood BMDL of 58 ug/L
  - 5^{th} percentile (lower 95^{th}) = 0.3 ug/kg/day
  - 1^{st} percentile (lower 99^{th}) = 0.2 ug/kg/day

- Using these doses as the starting point eliminates the need for a toxicokinetic UF factor (i.e., 3)

Database Insufficiency - UF_D

- Of the three major studies, two are positive for heart disease (MI etc.)
  - Finnish group (Salonen et al, 1995, etc.)
  - multicenter study (Guallar et al., 2002)
- One is (arguably) equivocal
  - U.S. Health Professionals (Yoshizawa et al., 2002)
- Should cardiovascular effects be addressed by a UF_D ?

MI - Myocardia Infarctio

Database Insufficiency–UF_D – cont'd

- To include UF for database uncertainty, it is only necessary that there be a reasonable basis for assuming that another endpoint could be more sensitive than the modeled endpoint.
  - **EPA generally accounts for lack of developmental and/or reproductive studies in RfD derivation <u>without supporting data</u>.**
- In the Finnish studies, the mean hair Hg conc. is approx. 2.0 ppm
  - **this is equivalent to approx 90^{th} percentile of U.S. adult men.**
  - **hair Hg >2.0 corresponded to a 1.96 relative risk for AMI**

AMI
ACUTE
MYOCARD
INFARCTIO

Database Insufficiency–UF_D – cont'd

- Yoshizawa et al. (U.S. Health Professionals) used toenail Hg as biomarker
  - cannot yet relate to hair or blood Hg
  - non-dentists presumably reflect general U.S. male population
    - mean = 0.45 +/- 0.4 ug/g

- Guallar et al. also used toenail Hg
  - elevated O.R. for MI clearly seen in range of 0.4-0.7 ug/g
  - corresponds to ~ mean Hg exposure in U.S. non-dentists
    - presumably corresponds to mean exposure in U.S. males

Database Insufficiency–UF_D – cont'd

- Therefore, it appears that for the two clearly positive studies, significantly elevated risk of MI occurred within the range of current dietary exposures of the U.S. adult male population

- This appears to justify application of a UF_D based on cardiovascular effects alone
  - a value of 2-3 appears to be appropriate
    - my judgment

Sensitive Humans - UF_H

- To include UF sensitive humans, it is only necessary that there be a reasonable basis for assuming that the U.S. population could have a greater range of sensitivity than the population from which the RfD was derived
- EPA (IRIS) used data from Faroes and NZ studies
  - Faroese are a homogeneous population
  - could result in more or less sensitivity than U.S. population
    - **e.g., founder effect**

Sensitive Humans – UF_H – cont'd

- NZ population is ethnically varied
  - 8% Europeans
  - 26% Maori
  - 66% Pacific Islanders

- Comparing Faroes and New Zealand studies:
  - standardized regression coefficients in NZ are about 41% larger
  - BMD values for NZ are about half those for Faroes
  - consistent with greater sensitivity due to ethnic diversity
    - but other explanations are also plausible

Sensitive Humans – UF_H – cont'd

- Homogeneity of Faroese, and possible greater sensitivity in the varied NZ population argues that U.S. population may have a greater range of sensitivity
- However, to some extent, the RfD is based on the NZ data
  - partly incorporates the greater sensitivity in that population
- At most, NZ population shows potential for about a 2-fold greater sensitivity
- This argues for a UF_H of only 1.5-2
  - my judgment

Some Possible Calculations (based on my own conclusions)

- Point of departure – maternal dose
  - corresponding to 58 ug/L
  - 1st (lower 99th) percentile incorporating cord:maternal and toxicokinetic variability
    - this is percentile used in current RfD
  - 0.2 ug/kg/day
- UF toxicodynamics (current EPA factor – default)
  - 3
- UF_H (sensitive populations - alternate toxicodynamic)
  - 1.5-2
- UF_D (cardiovascular)
  - 2-3

ug/L = 1 ppb

Some Possible Calculations (based on my own conclusions)

- Current EPA calculation
  (old dose conversion)
  - UF toxicokinetics = 3
  - UF toxicodynamica = 3

$$\frac{1.1\ \text{ug/kg/day}}{10} = 0.1\ \text{ug/kg/day}$$

Some Possible Calculations (based on my own conclusions)

- Using new dose conversion and EPA's current UF for toxicodynamics
  - i.e., $UF_H = 3$

$$\frac{0.2\ \text{ug/kg/day}}{3} = 0.07\ \text{ug/kg/day}$$

Some Possible Calculations (based on my own conclusions)

- Using new dose conversion,
- maximum UF_D and
- current EPA UF for toxiocdynamics
- UF_{total} (= 9)

$$\frac{0.2 \text{ ug/kg/day}}{3 \times 3} = 0.02 \text{ ug/kg/day}$$

Some Possible Calculations (based on my own conclusions)

- Using new dose conversion and
- minimum UF_D and UF_H
- UF_{total} (= 3)

$$\frac{0.2\ \text{ug/kg/day}}{2 \times 1.5} = 0.07\ \text{ug/kg/day}$$

- Other possible combinations fall in between

Conclusions - finally

- A fresh look at the UF for methylmercury incorporating new data and analyses presents a range of possible appropriate values for the resulting RfD
- These values extend from 70% of the current RfD to 20% of the current value
- There is no uniquely correct value, but this analysis presents a basis for a rational and transparent decision