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

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### RfD Derivation 101 – UFs

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- RfD = NOAEL (or LOAEL, or BMDL)  $(UF_1 \times UF_2 \dots UF_i)$
- UF = Uncertainty Factor

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

# RfD Derivation 101 – UFs – cont'd

- Uncertainty Factor categories
- $-UF_{\Lambda}$  animal  $\rightarrow$  human
- UF<sub>L</sub> LOAEL → NOAEL
- UF<sub>SC</sub> subchronic  $\rightarrow$  chronic
- UF<sub>H</sub> average humans -> sensitive humans
- UF<sub>D</sub> database insufficiency
- (UF<sub>M</sub> modifying factor)

# RfD Derivation 101 – UFs – cont'd

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

#### The Current RfD

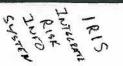
- UF = 10
- There are at least two new developments that could affect the appropriate value of the
- cord blood:maternal blood Hg ratio
- 1.7 (Stern and Smith, 2003)
- re-analysis of the maternal dose corresponding conversion") to the cord blood BMDL ("the dose
- (Stern, 2005)
- incorporates cord:maternal 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)
- sources of uncertainty The U.S.EPA reference dose for methylmercury:



# The Current RfD UF issues - cont'd

- These sources do not agree as to how and whether addressed in the UF for toxicokinetics the cord blood:maternal blood Hg ratio was
- If the dose conversion is now adjusted from a 1.0 3 for toxicokinetics need to be reduced to avoid cord:maternal ratio to a 1.7 ratio, would the UF of 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<sub>H</sub> (sensitive humans)

#### - IRIS

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

# The Current RfD-UF issues-cont'd

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



#### A Modest Proposal.

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



#### The Dose Conversion

- The dose conversion is derived probabilistically (Monte Carlo)
- dose corresponding to the cord blood BMDL captures the population variability in the maternal
- 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
- the BMDL can select the appropriate percentile of the distribution of maternal dose corresponding to
- e.g., 58 ug/L

## The Dose Conversion – cont'd

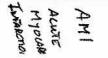
- Updated cord:maternal ratio (1.7) and its incorporated directly variability (Stern and Smith 2003) are
- Estimated maternal dose for a cord blood BMDL of 58 ug/L
- $5^{th}$  percentile (lower  $95^{th}$ ) = 0.3 ug/kg/day
- $1^{st}$  percentile (lower  $99^{th}$ ) = 0.2 ug/kg/day
- Using these doses as the starting point eliminates the need for a toxicokinetic UF factor (1.e., 3)

### Database Insufficiency - UFp

- 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<sub>D</sub>?

# Database Insufficiency-UF<sub>D</sub>-cont'd

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



# Database Insufficiency-UF<sub>D</sub>-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
- 0.4-0.7 ug/g elevated O.R. for MI clearly seen in range of
- corresponds to ~ mean Hg exposure in U.S non-dentists
- presumably corresponds to mean exposure in U.S.

# Database Insufficiency-UF<sub>D</sub>-cont'd

- Therefore, it appears that for the two clearly population dietary exposures of the U.S. adult male of MI occurred within the range of current positive studies, significantly elevated risk
- This appears to justify application of a UF<sub>D</sub> based on cardiovascular effects alone
- a value of 2-3 appears to be appropriate
- my judgment



### Sensitive Humans - UFH

- To include UF sensitive humans, it is only have a greater range of sensitivity than the for assuming that the U.S. population could necessary that there be a reasonable basis 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<sub>H</sub> –

- 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<sub>H</sub> – cont'd

- Homogeneity of Faroese, and possible greater sensitivity sensitivity in the varied NZ population argues that U.S. population may have a greater range of
- 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<sub>H</sub> 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
- 1<sup>st</sup> (lower 99<sup>th</sup>) 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)
- UF<sub>H</sub> (sensitive populations alternate toxicodynamic)
- -1.5-2
- UF<sub>D</sub> (cardiovascular)

#### Some Possible Calculations (based on my own conclusions)

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

1.1 ug/kg/day = 0.1 ug/kg/day

#### Some Possible Calculations (based on my own conclusions)

 Using new dose conversion and EPA's current UF for toxicodynamics

$$- i.e., UF_{H} = 3$$
  
 $0.2 \text{ ug/kg/day} = 0.07 \text{ ug/kg/day}$ 

#### Some Possible Calculations (based on my own conclusions)

- Using new dose conversion,
- maximum UF<sub>D</sub> and
- current EPA UF for toxiocdynamics
- $\frac{\text{UF}_{\text{total}} (= 9)}{0.2 \text{ ug/kg/day}} = 0.02 \text{ ug/kg/day}$  $3 \times 3$

#### Some Possible Calculations (based on my own conclusions)

- Using new dose conversion and
- minimum UF<sub>D</sub> and UF<sub>H</sub>
- $UF_{total} (= 3)$  0.2 ug/kg/day = 0.07 ug/kg/day $2 \times 1.5$
- Other possible combinations fall in between

#### Conclusions - finally

- resulting RfD range of possible appropriate values for the A fresh look at the UF for methylmercury incorporating new data and analyses presents a
- 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