A Probabilistic Hazard Characterization Framework for Addressing Uncertainty and Variability

Monday 9 January 2017
National Academy of Sciences
Workshop on Guiding Principles for the Inclusion of Chronic Diseases

Weihsueh A. Chiu, PhD
(Consultant to the Committee)
Texas A&M University
Neither myself nor any of my coauthors, including members of our immediate families, have any financial interest or affiliation with a commercial organization that has a direct or indirect interest in the subject matter of my presentation.
Acknowledgments

• Final WHO/IPCS Author Group
  – Bernard Bottex, EFSA representative
  – David Bussard, U.S. EPA
  – Weihsueh Chiu, formerly U.S. EPA
  – George Fotakis, ECHA representative
  – Andy Hart, FERA, UK
  – Dale Hattis, Clark University, USA
  – Matthias Herzler, BfR, Germany
  – Kathy Hughes, IPCS
  – Wout Slob, RIVM, Netherlands
  – Theo Vermeire, RIVM, Netherlands
  – Carolyn Vickers, IPCS

• Other colleagues
  – Frederic Bois, INERIS
  – Kenny Crump, consultant
  – Gary Ginsberg, Conn. DEPH
  – Greg Paoli, RSI
  – Woody Setzer, U.S. EPA
  – Lauren Zeise, California EPA
WHO/IPCS Project on Uncertainty in Hazard Characterization

- Proposal accepted in 2008.
- Periodic conference calls between meetings.
- Peer review workshop in November 2013.
- Involved approximately 45 scientists and representatives of ECHA and EFSA.
- Guidance Document Published Sept 2014
  - Harmonization Project Document No. 11
  - APROBA spreadsheet tool
- Training Course at EUROTOX in Sept 2015
- Methods published in EHP in Dec 2015
- Continuing Education Workshop at Society for Risk Analysis meeting in Dec 2016

http://www.who.int/ipcs/methods/harmonization/areas/hazard_assessment/en/
Outline

• Limitations in Traditional Approach to Deriving DRI UL values

• Five Steps to “Modernizing” the UL Using Probabilistic Approaches
  1. Replace NOAEL/LOAEL with Benchmark Dose
  2. Replace Inter-species Uncertainty Factor with Distribution
  3. Replace Intra-species Uncertainty Factor with Distribution
  4. Derive a more transparent “Probabilistic UL”
  5. Derive a more informative “Probabilistic Intake-Response Function”

• Example with Boron

• Opportunities and Challenges
Conceptual Model for DRI values

Risk of Adverse Effect (Deficiency)

Risk of Adverse Effect (Toxicity)

Deficiency

RDA

UL

Focus Today

Intake
Limitations of Traditional Approach to Deriving DRI UL Values

\[ UL = \frac{NOAEL}{UF_A \times UF_H} \]

- What is the size of the potential effect?
- Factors assumed to be conservative, but unclear by how much.
- Assumed to be conservative, but unclear by how much.
- No estimate of residual or incremental risks.

\[ NOAEL \times UF_A \times UF_H \]

Traditional Approach

Divide by inter-species factor

Divide by intra-species factor

DRI Upper Level

**Percent Incidence of Response**

<table>
<thead>
<tr>
<th>Dose</th>
<th>0</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LOAEL**

**NOAEL**

**Intake**

**Magnitude of response**

**Intra**

**Inter**
Outline

• Limitations in Traditional Approach to Deriving DRI UL values

• Five Steps to “Modernizing” the UL Using Probabilistic Approaches
  1. Replace NOAEL/LOAEL with Benchmark Dose
  2. Replace Inter-species Uncertainty Factor with Distribution
  3. Replace Intra-species Uncertainty Factor with Distribution
  4. Derive a more transparent “Probabilistic UL”
  5. Derive a more informative “Probabilistic Intake-Response Function”

• Example with Boron

• Opportunities and Challenges
NOAEL is the Usual Starting Point for Deriving DRI UL Values

- **NOAEL**: Greatest concentration or amount of a substance, found by experiment or observation, that causes no adverse alteration ...of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.*

- Used as “point of departure” for deriving toxicity values such as DRI Upper Levels.

- Commonly viewed *(incorrectly)* as an experimental dose threshold.

- **LOAEL**: Lowest dose in the study above the NOAEL (or above the control if no NOAEL is identified)

*WHO definition*
Issues with NOAEL

• Limited to doses in the study
Issues with NOAEL

- Limited to doses in the study
- Minimum detectable response \textbf{increases} as sample size \textbf{decreases}
- Role of expert judgment often unclear
- Not comparable across studies
- \textbf{Conceptually undefined} – definition tied to a particular study
Replacing the NOAEL with the Benchmark Dose (BMD)*

- Fitting a curve, so not limited to doses in the study

- Magnitude of response fixed at a “benchmark response” (BMR)
  - Clarifies role of expert judgment
  - Avoids misinterpretation as “threshold”
  - Aids comparability across studies
  - Appropriately accounts for statistical uncertainty

*Crump (1984)
Replacing the NOAEL with the Benchmark Dose (BMD)*

• Fitting a curve, so not limited to doses in the study

• Magnitude of response fixed at a “benchmark response” (BMR)
  – Clarifies role of expert judgment
  – Avoids misinterpretation as “threshold”
  – Aids comparability across studies
  – Appropriately accounts for statistical uncertainty

• Well-defined conceptually, independent of specific dataset

*Crump (1984)
Benefits are a consequence of the BMD having a more precise definition than the NOAEL

**NOAEL:**
Greatest concentration or amount of a substance, found by experiment or observation, that causes no adverse alteration ... of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

**BMDL:**
A statistical lower confidence limit on the dose that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.

NOAEL should be viewed as an “approximation” of the BMD!
Risk Assessment Community Views Benchmark Dose as More Scientifically Valid than NOAEL

- European Food Safety Authority Scientific Opinion (2009)

Still have work to do…
Modernizing DRI UL Derivation Step 1: Replacing NOAEL with BMD

\[ UL = \frac{BMD_{BMR}}{UFA \times UFH} \]

- Magnitude of effect specified by BMR
- Factors assumed to be conservative, but unclear by how much.
- Assumed to be conservative, but unclear by how much.
- No estimate of residual or incremental risks.

Magnitude of response

Intake

UL

BMD

BMDL

LOAEL

BMR

NOAEL

Intra

Inter
What do “Uncertainty Factors” really mean?

• What does an **interspecies uncertainty factor of 10** mean?

  Humans are 10x more sensitive than experimental animals

  **For most compounds and endpoints,** humans are no more than 10x more sensitive than experimental animals

• Thus, the factor of 10 is intended to cover “most” cases, i.e., the “true” interspecies differences most likely will be ≤10.

  “most likely” = 90%? 95%? 99%?

  10 is somewhere over here

  (Humans may be less sensitive than experimental animals)

  0.1 is somewhere over here

  True interspecies ratio
What Do We Known About Interspecies Differences from Historical Data?

• On average, species are equally sensitive after adjusting for body size (allometric scaling).
• After adjusting for body size, there is still compound-to-compound variability due to case-specific pharmacokinetics/dynamics.

Separate into two factors:

\[
UF_{A-BS} = \left\{ \frac{bw_{human}}{bw_{test\ species}} \right\}^{1 - \alpha}
\]

\[
UF_{A-PK/PD} = \text{"scatter" after adjusting for body size}
\]

Estimate uncertainty distributions for \(\alpha\) and \(UF_{Inter-PK/PD}\) from historical data.

Results Based on Historical Data for Interspecies Uncertainty Factor

Uncertainty in body size adjustments
- E.g., rat-to-human:
- \((\frac{bw_{human}}{bw_{rat}})^{1-\alpha}\)
- \(\alpha \sim N(0.70, 0.024)\)

Uncertainty in compound-specific PK/PD
- Due to compound-to-compound variation

Source: Based on analysis by Bokkers and Slob (2007)
Modernizing DRI UL Derivation Step 2: Replacing $UF_A$ with Two Distributions

- Allometric scaling
- Remaining PK/PD differences
- Assumed to be conservative, but unclear by how much.
- No estimate of residual or incremental risks.

**Updated Approach**

$UL = \frac{BMD_{BMR}}{UF_A \times UF_H}$

$UF_A = UF_{A_{abs}} \times UF_{APKPD}$

**DRI Upper Level**

**BMD**

**BMDL**

**BMR**

**Intra**

**Inter**

**Magnitude of response**

**Intake**
Similar Approach with Intra-species Uncertainty Factor (Human Variability)

• **What does a** human variability uncertainty factor of 10 **mean?**

  The range from “least sensitive” to “most sensitive” humans is 10-fold.

  “Sensitive” humans are 10x more sensitive than “typical” humans.

  For most chemicals and endpoints, “sensitive” humans are no more than 10x more sensitive than “typical” humans.

• **Thus, the factor of 10 is intended to cover “most” chemicals for “sensitive” humans** – i.e., in most cases, the factor covering “sensitive” will be ≤10.

  (By definition of “sensitive,” has to be >1)
Variability distribution is approximately lognormal: 
**Interindividual variability, GSD\(_H\)**

Human equipotent dose

\(i^{th}\) percentile defines “sensitive” individual being protected (e.g., 1\(^{st}\) percentile)

\(UF_{H-I} = GSD_H^{ |z_i|} \)

Uncertainty distribution for \(UF_{H-I}\)

Estimates of Log\((GSD_H)\) for historical data on different compounds*

Uncertainty distribution is approximately lognormal: **Compound-specific uncertainty, GSD\(_U\)**

Uncertainty distribution (depends on choice of \(i!\))

Modernizing DRI UL Derivation Step 3: Replacing $\text{UF}_H$ with Distribution At Incidence /

$\text{UL} = \frac{\text{BMD}_{\text{BMR}}}{\text{UF}_A \times \text{UF}_{H_1}}$

$\text{UF}_A = \text{UF}_{A_{\text{abs}}} \times \text{UF}_{A_{\text{PKPD}}}$

- Probability distributions disaggregating uncertainty and variability
  - Assumed to be conservative, but unclear by how much.
  - No estimate of **residual** or **incremental** risks.

Updated Approach

- Divide by inter-species distributions
- Divide by intra-species distribution

**DRI Upper Level**

**BMD**

**BMDL**

**BMR**

**UL**

**Intake**

Magnitude of response
Modernizing DRI UL Derivation Step 4:
Replacing UL with a Probabilistic UL

\[
UL = \frac{BMD_{BMR}}{UF_A \times UF_{H_I}}
\]

\[
UF_A = UF_{A_{bs}} \times UF_{A_{PKPD}}
\]

- Probability distributions disaggregating uncertainty and variability
- Probabilistic DRI is an uncertainty distribution at a magnitude \((M=BMR)\) and incidence \((I)\) of response.

Updated Approach

- \(BMD_{BMR}\)
- Divide by inter-species distributions
- Divide by intra-species distribution
- Probabilistic DRI UL

Magnitude of response vs. Intake

- BMD
- BMDL
- BMR
- UL

Intra vs. Inter

24
Modernizing DRI UL Derivation Step 4: Replacing UL with a Probabilistic UL\(_{M}^I\)

**Tolerable Upper Intake Level UL:**
The highest level of daily nutrient intake that is *likely* to pose *no risk of adverse health effects* to *almost all individuals in the general population*.

**Probabilistic UL:**
A statistical lower confidence limit on the daily nutrient intake at which *a no more than fraction I of the population* shows an *effect of magnitude M or greater*.

Traditionally-derived UL should be viewed as an “approximation” of a Probabilistic UL!
Modernizing DRI UL Derivation Step 5:

Treating $UL_M^I$ as an Intake-Response Function

$$UL_M^{I=BMR} = \frac{BMD_{BMR}}{UF_A \times UF_{H_i}}$$

$$UF_A = UF_{A_{bs}} \times UF_{A_{PKPD}}$$

- More fully characterizes intake-response
- Makes policy judgments more explicit ($M$, $I$, percent confidence)
- After BMD modeling, data requirements same as “traditional” UL.

![Graph showing the relationship between intake and magnitude of response.](image)
Outline

• Limitations in Traditional Approach to Deriving DRI UL values

• Five Steps to “Modernizing” the UL Using Probabilistic Approaches
  1. Replace NOAEL/LOAEL with Benchmark Dose
  2. Replace Inter-species Uncertainty Factor with Distribution
  3. Replace Intra-species Uncertainty Factor with Distribution
  4. Derive a more transparent “Probabilistic UL”
  5. Derive a more informative “Probabilistic Intake-Response Function”

• Example with Boron

• Opportunities and Challenges
Boron DRI (NAS, 2001) based on NOAEL

- Reduced fetal BW in rats
  - UL = NOAEL x BW / (UF_A x UF_H)
  - NOAEL = 9.6 mg/kg-d
  - BW = 61 kg (pregnant women)
  - UF_A = 10 (default)
  - UF_H = 3 (reduced from 10 due to expected similarities in PK)
  - UL = 9.6 x 61 / 30 = 20 mg/d
Boron EPA (2004) RfD based on BMDL (Step 1) and Boron PK data

- **Reduced fetal BW in rats**
  - $RfD = \frac{BMDL_{05}}{(UF_{A-TK} \times UF_{A-TD} \times UF_{H-TK} \times UF_{H-TD})}$
  - $BMDL_{05} = 10.3 \text{ mg/kg-d}$
  - $UF_{A-TK} = 3.3$ (rat-human PK)
  - $UF_{A-TD} = 10^{\frac{1}{2}}$ (default)
  - $UF_{H-TK} = 2$ (3-sd PK difference among pregnant women)
  - $UF_{H-TD} = 10^{\frac{1}{2}}$ (default)
- $RfD = \frac{10.3}{66} = 0.16 \text{ mg/kg-d}$
- $RfD \times 61 \text{ kg} = 9.5 \text{ mg/d}$
Probabilistic Boron UL:
Steps 1 (BMD) and 2 (UF_A)

Inter-species adjustment to median human
Distribution of model fits

% Decrease in fetal weight (median human)

Boron Dose (mg/kg-d)
Fetal Weight (g, litter mean and se)

Human Boron Dose (mg/kg-d)
Probabilistic Boron UL:
Step 3 (UF_H)

- Inter-species adjustment to median human
- Intra-species adjustment to 1%ile human

Distribution of model fits

% Decrease in fetal weight (1% most sensitive human)

Boron Dose (mg/kg-d)

Fetal Weight (g, litter mean and se)

Human Boron Dose (mg/kg-d)

Price et al., Heindel et al.

NOAEL, UCL, Fit, LCL

0% 2% 4% 6% 8% 10%

0.01 0.1 1 10
Probabilistic Boron UL: Steps 4 and 5 ($UL_M^I$ as point and function)

- **Point estimate** gives the intake in pregnant women at which
  - With 95% confidence
  - Less than $I=1\%$ of pregnant women
  - Will experience a $M=5\%$ decrease in fetal weight
- Other choices of $I$ and $M$ could be made – values are transparent
- **Full intake-response function** for toxicity also estimated, with confidence bounds

0.12 mg/kg-d $\rightarrow$ 7 mg/d for 61 kg pregnant woman

% Decrease in fetal weight (1% most sensitive human)

- $0\%$ Decrease in fetal weight
- $1\%$ Decrease in fetal weight
- $2\%$ Decrease in fetal weight
- $4\%$ Decrease in fetal weight
- $6\%$ Decrease in fetal weight
- $8\%$ Decrease in fetal weight
- $10\%$ Decrease in fetal weight

Human Boron Dose (mg/kg-d)

- $0.01$ mg/kg-d
- $0.1$ mg/kg-d
- $1$ mg/kg-d
- $10$ mg/kg-d
Result is closer to the original DRI conceptual model

Risk of Adverse Effect (Deficiency)

Intake

Deficiency

RDA

UL

Risk of Adverse Effect (Toxicity)

% Decrease in fetal weight (1% most sensitive human)

% Decrease in fetal weight

UCL

Fit

LCL

Human Boron Dose (mg/kg-d)
Opportunities and Challenges

Key Opportunities of Probabilistic UL

• Forms a more rigorous and transparent basis for UL
• Better characterizes uncertainty and variability
• Provides complete intake-response function in keeping with DRI conceptual model
• Enables assessment of risk-benefit and risk-risk tradeoffs
• Potential application to other DRIs values (RDAs, chronic disease)
Opportunities and Challenges

Key Challenges of Probabilistic UL

- Lack of experience/training with probabilistic methods.
- Communicating residual risk & uncertainty is difficult.
- Existing efforts focused on toxicity of contaminants / toxins, not essential nutrients.
- Limited experience with incorporating compound-specific data.
- Approach has not (yet) been applied to human epidemiologic data.
Summary

• Traditional approach to derive DRI UL values has a number of limitations in terms of transparency and utility.

• Methods and data incorporated into WHO/IPCS guidance can address these limitations by deriving a “Probabilistic UL”:
  – Point estimate as a traditional “bright line” value
  – Intake-response function to better inform tradeoffs

• Approach can be readily implemented for UL values based on experimental animal toxicology data, as illustrated in the Boron example.

• Opportunities and challenges for broader application.