Uncertainty Analysis - A Necessity for Transparency

Energy lives here
• **Background**

• **Overview of uncertainty analyses tool**

• **Implications outside of risk management**
Final Risk Values can Imply False Precision

Risk Assessment

Final Risk Value
Risk Characterization Ratio (RCR)
Hazard Quotient (HQ)
Hazard Index (HI)

>1 = risk
<1 = no risk

Risk Management
How is the excess risk controlled?
Final Risk Values can Imply False Precision

The 4 Step Risk Assessment Process

- **Exposure Assessment**: How many and how much are people exposed at a specific time?
- **Risk Characterization**: Chance of adverse health effect?
- **Risk Management**: How is the excess risk controlled?

- **Hazard Identification**: Potential health effects
- **Dose-Response Assessment**: Health effects at different doses

>1 = risk
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Risk Assessment

Final Risk Value
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Risk Management
How is the excess risk controlled?
ACC ARASP* Uncertainty Communication Workshop
Nov 2013

• Focus on identification of sources & communication of uncertainty in human health risk assessment
  • Not how to measure
  • Not quantitative analysis methods

• Uncertainty = lack or incompleteness of information
  • Can be reduced or eliminated with more or better data

• Variability = heterogeneity or diversity in attributes
  • Cannot be reduced, but can be better characterized

• Example: body weight – can better characterize with more data (uncertainty), but cannot decrease heterogeneity in the population (variability)

*American Chemistry Council's Center for the Advancement of Risk Assessment Science and Policy
ACC ARASP* Uncertainty Communication Workshop

• How best to communicate uncertainty
  • Different types (sources; magnitudes)
  • Different impact on results of assessment
  • Different audiences

• Communication tools should be:
  • Transparent
    • Distinguish science judgment from science policy
  • Comprehensible
    • Simplify complex concepts
  • Useful
    • Geared towards identified audience (Risk Managers & the public)
Improving Transparency in Dose-Response Decision Making

- Detailed focus on individual assessment
- Analysis of key decisions – data and other; distinguishes science from policy
- Original format did not incorporate other aspects of risk assessment

Without uncertainty a Point of Departure selection lacks context

- At the end of an RA the selected PoD is provided as a numerical value with text description.
- 50 mg/kg/d based on NOAEL for developmental endpoints
Showing Uncertainty in Risk Assessment decision better conveys the state of the data

Example 1 – Final Risk Characterization Ratio (RCR) of 0.97 or 1.96
  Risk manager: Decision could not “exclude” risk based on numerical RCR values

Example 2 – Hazard Index Values (2005/06): 12.2, 7.4, and 7.3
  Risk manager: Draft rule to extend ban based on numerical HI values
Showing Uncertainty in Risk Assessment decision better conveys the state of the data

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  Risk manager: Decision could not “exclude” risk based on numerical RCR values

Transparent communication of uncertainty in RCR derivation –
  Regulatory threshold for concern set at RCR value of 1

RCR values (0.97 & 1.96) calculated using the most conservative assumption at each decision point

Risk Values based on normalization of the data to central tendency value (i.e. RCR/central tendency RCR)
Showing Uncertainty in Risk Assessment decision better conveys the state of the data

Example 1 – Final Risk Characterization Ratio (RCR) of 0.97 or 1.96
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Transparent communication of uncertainty in RCR derivation –
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RCR values (0.97 & 1.96) calculated using the most conservative assumption at each decision point

RCR value (0.004) calculated using the central tendency of risk assessment decision points

Risk Values based on normalization of the data to central tendency value (i.e. RCR/central tendency RCR)
Showing Uncertainty in Risk Assessment decision better conveys the state of the data

Example 2 – Hazard Index Values (2005/06): 12.2, 7.4, and 7.3
Risk manager: Draft rule to extend ban

Communication of uncertainty in HI derivation and impact of alternative data –
Regulatory threshold for concern set at HI value of 1

HI values (12.2, 7.4, and 7.3) using 95th percentile exposure information from 2005/2006

Risk Values based on normalization of the data to regulatory risk value (i.e. HI/HI indicating risk)
Communication of uncertainty in HI derivation and impact of alternative data – Regulatory threshold for concern set at HI value of 1

Example 2 – Hazard Index Values (2005/06): 12.2, 7.4, and 7.3
Risk manager: Draft rule to extend ban

HI values (12.2, 7.4, and 7.3) using 95th percentile exposure information from 2005/2006

HI value (0.23) calculated using the 95th percentile exposure information from 2011/2012

Risk Values based on normalization of the data to regulatory risk value (i.e. HI/HI indicating risk)
Every Decision in a RA Involves Uncertainty

- Each decision point can be evaluated/depicted independently
  - Transparent depiction of range of data
Application of methodology to CPSC Cumulative Risk Assessment
Showing Uncertainty in the Point of Departure Selection

- Data is normalized to 1
  - Central tendency of data – mean, median, mode (objective)
  - Other scientifically valid value (expert judgment or subjective)
  - Designated in column 3 (i.e. “Baseline”)
- Range of all the data (e.g. all NOAELs) is shown as a blue horizontal bar
- Closed triangles are the values selected in the assessment
- Modelled data (green triangle) clearly is not supported by the experimental data

### Decision Point
<table>
<thead>
<tr>
<th>Range of Options**</th>
<th>Baseline (dashed line)</th>
<th>Selected in Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.000001 0.00001 0.0001 0.01 0.1 10 100 1000</td>
<td></td>
</tr>
<tr>
<td>Data Set/Endpoint Selection* Anogenital Distance (AGD)</td>
<td>Normalized to selected endpoint</td>
<td>NOAEL selected based on testosterone decrease</td>
</tr>
<tr>
<td>Data Set/Endpoint Selection* Reproductive Organ Abnormalities</td>
<td>Normalized to selected endpoint - no statistically significant effect in highest dose tested</td>
<td>NOAEL selected based on testosterone decrease</td>
</tr>
<tr>
<td>Data Set/Endpoint Selection* Testosterone</td>
<td>Avg NOAEL of studies evaluating endpoint</td>
<td>NOAEL selected for DINP by CHAP Lowest available PoD for endpoint selected</td>
</tr>
<tr>
<td>Data Set/Endpoint Selection* Nipple Retention (NR)</td>
<td>Normalized to selected endpoint</td>
<td>NOAEL selected based on testosterone decrease</td>
</tr>
<tr>
<td>Data Set/Endpoint Selection* Reproductive Organ Weight</td>
<td>Normalized to selected endpoint</td>
<td>NOAEL selected based on testosterone decrease</td>
</tr>
<tr>
<td>PoD Selection*</td>
<td>Normalized to selected endpoint</td>
<td>Case 1: 750 mg/kg/d</td>
</tr>
<tr>
<td></td>
<td>Normalized to selected endpoint</td>
<td>Case 2: 11.5 mg/kg/d</td>
</tr>
<tr>
<td></td>
<td>Normalized to selected endpoint</td>
<td>Case 3: 50 mg/kg/d</td>
</tr>
</tbody>
</table>
Can identify patterns in the data
- Visually depicts potency differences across chemicals
- The basis for modelled data (△) is only accurate for single chemical

Alternative decision points can be added
- PoD for reproductive tract malformations (RTM) across all chemicals

Data Set/Endpoint Selection* DBP
NOAEL for AGD/NR

Data Set/Endpoint Selection* DIBP
NOAEL AGD

Data Set/Endpoint Selection* BBP
NOAEL for AGD/NR

Data Set/Endpoint Selection* DEHP
NOAEL for RTM/DSS

Data Set/Endpoint Selection* DINP
NOAEL for testosterone decrease (TT) and MNG
Can Highlight Potential Impact of Changes

- Range of exposure values from NHANES biomonitoring data (2005/2006)
  - ▲ – 99th percentile 2005/06 data set
  - △ – 99th percentile 2011/12 data set

- Demonstrates change in exposure trends
  - Probable impact on risk assessment
Comparison of Risk Estimates Across Five Compounds in a Cumulative Risk Assessment

- Four of the five risk estimates fall below identified risk management level
- Cumulative risk estimate (last line) is nearly identical to risk estimate for single compound

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hazard Quotient*</th>
<th>Hazard Index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEHP</td>
<td></td>
<td></td>
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<td>DINP</td>
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</table>
Clearly displays effect on risk estimate when input value is changed.
Clearly displays effect on risk estimate when input value is changed

Risk estimates separate
Greater impact of decision point due to shift in exposure estimates. Clearly displays effect on risk estimate when input value is changed. Risk estimates separate.
Clearly displays effect on risk estimate when input value is changed

Greater impact of decision point due to shift in exposure estimates

Understanding basis of “cases” becomes more important
Understanding basis of “cases” becomes more important depending on policy decision (i.e. exposure percentile), risk estimate could convey need for alternative decision.
Holistic view of RA conveys more information than point estimates.

- **PoD Selection***
- **Interspecies Variation (UFa)***
- **Intraspecies Variation (UFh)**
- **Composite UF***
- **Potency Estimate for Anti-androgenicity "PEAA"***

**Ability to track impact across tool-decision points across Case 1**

**Capture distribution of exposure data and hazard values**

**Plot risk value based on central tendency**

**Compare central tendency of data to RA outcomes**
Holistic view of RA conveys more information than point estimates

Ability to add new information and track impact across tool

Example – impact of human xenograft data on interspecies

Single compound specific data depicted

ExxonMobil
Decision Point Baseline (dashed line) Selected in Risk Assessment

Mode of Action Assessment*
- Reproductive toxicity
- Liver toxicity

Data Set/Endpoint Selection*
- Anogenital Distance (AGD)
- Reproductive Organ Abnormalities
- Testosterone
- Nipple Retention (NR)
- Reproductive Organ Weight

PoD Selection*

Interspecies Variation (UFa)*

Intraspecies Variation (UFh)

Composite UF*

Potency Estimate for Anti-androgenicity "PEAA**

Exposure

Hazard Quotient*

Hazard Index*

Human relevance of PoD/appropriate for human risk assessment
PoD associated with anti androgenicity, NOAEL selected based on testosterone decrease

Normalized to selected endpoint
NOAEL selected based on testosterone decrease

Normalized to selected endpoint - no statistically significant effect in highest dose tested
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Normalized to selected endpoint
Case 1: 750 mg/kg/d
Case 2: 11.5 mg/kg/d
Case 3: 50 mg/kg/d

Xenograft data & marmoset data suggest humans are likely less sensitive than rats if not refractory to the effects
10 (assume that humans are 10x more sensitive than rats)

Evaluations of variation in populations suggest 5 is more appropriate (ECETOC)
10 (assume some individuals are 10x more sensitive)

Assumes animal data would be predictive of any potential sensitive subpopulation
Case 1: 200  Case 2: 100 Case 3:100

Predictive NOAEL divide by composite UF accounting for differences in rat/human sensitivity for endpoint
50th percentile 2011/2012 WoRA 99th percentile 2005/2006 Preg

HQ 50th percentile 2011/2012 Case 3, WoRA
HQ 99th percentile 2005/2006 Case 3, Preg

Hi 50th percentile 2011/2012 Case 3, WoRA
Hi 99th percentile 2005/2006 Case 3, Preg

Range of Options**
- 0.000001
- 0.00001
- 0.0001
- 0.001
- 0.01
- 0.1
- 1
- 10
- 100
- 1000
Conclusions

• Visualization of data included in the risk assessment:
  • Increases transparency of the data set
  • Clearly indicates how altering each decision point would affect the outcome
  • Gives a holistic view of the entire data set
  • Indicates range of data for each decision point, which can help depict uncertainty/variability in the data

• This methodology can help depict whether the uncertainty/variability in the entire dataset supports the final conclusion.

• Provides a relatively easy manner to present information to a risk manager to make a better informed decision

• Important component of transparency, which is critical for scientific dialogue and progress
Development of tool into user friendly interface

- Tool currently exists in an excel spreadsheet format
- Collaborating with external organization to transfer concept to publically accessible format
Analysis Metadata

- Analysis Name: Tool Demonstration
- Risk assessment decision: Case 1
- Risk assessment decision: Case 2
- Add Additional Decision
- Hazard/Mode of Action: Developmental toxicity
- Units: mg/kg/day
- Histogram Source: LOAEL/NOAEL

- Dose-Response Assessment - Analysis POD
- Dose-Response Assessment - Endpoint-Level PODs
- Dose-Response Assessment - Uncertainty Factors
- Dose-Response Assessment - Potency Estimates
- Exposure Assessment
- Risk Characterization
## Dose-Response Assessment - Analysis POD

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg/day</td>
<td>4 mg/kg/day</td>
</tr>
</tbody>
</table>

Analysis minimum value: 1
Analysis maximum value: 88

Normalization: anogenital 12.5 mg/kg/day
Individual study record data can be inputted into the tool

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>LOAEL</th>
<th>NOAEL</th>
<th>BMDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feiler et al, 2017</td>
<td>20 mg/kg/day</td>
<td>9 mg/kg/day</td>
<td>13 mg/kg/day</td>
</tr>
<tr>
<td>X Wignall et al, 2017</td>
<td>7 mg/kg/day</td>
<td>5 mg/kg/day</td>
<td>6 mg/kg/day</td>
</tr>
<tr>
<td>X Feiler et al, 1999</td>
<td>24 mg/kg/day</td>
<td>16 mg/kg/day</td>
<td>20 mg/kg/day</td>
</tr>
<tr>
<td>X Feiler et al, 2001</td>
<td>50 mg/kg/day</td>
<td></td>
<td></td>
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</table>
Selected uncertainty factors can be added and individualized for each case

- Deselection of uncertainty factors would prompt tool to display Margin of Exposure for risk characterization

<table>
<thead>
<tr>
<th>Interspecies Variation (UFA)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>X</td>
<td>1</td>
<td>10</td>
<td>10</td>
<td>4</td>
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<td>1</td>
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<td>6</td>
<td>7</td>
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</table>
Potency estimates or reference/acceptable/tolerable intakes are automatically calculated based on previous inputs.

Will need to harmonize the language or provide drop down selections (i.e. RfD, DNEL, MoS etc...)
Tool automatically generates and updates visualization based on inputs.
Next Steps

• Continue building tool to incorporate exposure and risk characterization

• Improve graphical interface

• Test tool with small user base and incorporate feedback

• Test more complex input data
  • monte carlo simulations
  • Exposure scenarios
    • worker vs consumer

• Scope ability to draw data from other sources
  • i.e. interface with HAWC