Quantitative Evaluation of Uncertainty: APROBA and Beyond

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Purpose and Scope

Quantitative assessment of uncertainty was recommended by the NRC:

- *Science and Decisions* report (NRC, 2009) – recommended incorporating probabilistic methods for assessing uncertainty.
- *Review of the IRIS Program* report (NRC, 2014) – recommended systematic use of uncertainty analysis and expanded use of Bayesian methods.

NCEA will pilot this approach to better understand issues in implementing it and to engage in dialogue with stakeholders as to advantages and challenges in utilizing this approach.

Probabilistic Calculation of Risk-Specific Doses

Goal: Probabilistically incorporate adjustments and uncertainty when extrapolating dose-response results from animal data to the human population.

Current Practice: Reference values (RfVs) are generally calculated by dividing a point of departure (POD; usually a BMDL or NOAEL) by a series of uncertainty factors (UFs):

$$\mathrm{UiY} = \frac{\mathrm{SRG}}{\mathrm{UI}_1 \times \cdots \times \mathrm{UI}_k}$$

- Default values of UFs are (1, 3, or 10).
- Decision on which value to use is made qualitatively based on information available for the particular assessment (e.g., size of database, study characteristics)
- Reference Value definition does not explicitly target incidence, effect size, or confidence.

Proposed New Practice: Calculate risk-specific dose intervals using probabilistically-defined versions of POD and UFs, using the concept of target human dose.

Target Human Dose and APROBA

Target human dose, HD_M^I:

- HD_M^I = the Human Dose at which a fraction (or incidence) I of the population shows an effect of magnitude (or severity) M or greater for the critical effect considered.
  - A "risk-specific dose."

Examples:

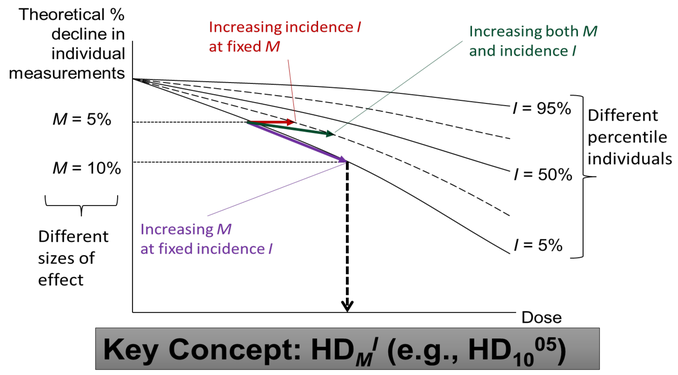
- HD_{10}^{01} = human dose at which 1% of the population shows an increase in liver weight of 10% or greater above background.
- HD_{05}^{01} = human dose at which there is an individual extra risk of lung tumors of 5% (or more) in 1% of the population.

HD_M^I is calculated using the formula similar to RfV:

$$\mathrm{KG}_M^{\ I} = \frac{\mathrm{SRG}}{\mathrm{DI}_1 \times \cdots \times \mathrm{DI}_k} \qquad (1)$$

- Each AF, or "assessment factor," is treated as a continuous random variable; the parameters of the distributions of these random variables can be determined from empirical data. The resulting HD_M^I is a random variable with its own probability distribution.

Target Human Dose (cont'd)



Key Concept: HD_M^I (e.g., HD_{10}^{05})

Approximate Probability Analysis (APROBA) is an Excel-based tool to calculate a probabilistic RfV from animal data.

- Computes HD_M^I under the assumption that the POD and AFs are independent lognormally distributed.
- An analogue to a reference value can be derived for a pre-selected percentile (e.g., 5th percentile) of the HD_M^I distribution. The interval reflects uncertainty as well as a choice of a desired confidence (e.g., 95%) in the HD_M^I estimate.
- Was applied by the Dutch National Institute for Public Health and the Environment (RIVM) in recent risk assessment on melamine.

Example

Dose-response data of absolute epididymis weight in adult rats after exposure to chemical X by inhalation:

Exposure (ppm)	No. of animals	Mean (mg)	SD (mg)
0	25	0.3327	0.03631
100	25	0.3311	0.04453
250	25	0.3053	0.04188
500	25	0.2912	0.05206
750	25	0.2405	0.04804

Exponential model 3 fit to data at BMR of 10% relative deviation from control mean yields: BMDL = 237 ppm; BMDU = 535 ppm

Input in APROBA worksheet:

INPUTS RELATED TO STUDY, END-POINT AND PROTECTION GOALS	
DESCRIPTION	**INPUTS**
End-point	Absolute epididymal weight
Data type	Continuous
Data route	Inhalation
Study type	Subchronic
Test species	Rat
Body weight test species (kg)	0.4
Human median body weight (kg)	60
Target BMR (= *M*, user input for BMDLs only)	10%
Population incidence goal (= *I*)	1%
Probabilistic coverage goal	95%
PoD type	BMDL
PoD value	237
BMDU (User input for BMDL PoDs)	535
PoD units	mg/cu. m

INPUTS RELATED TO ADJUSTMENT, VARIABILITY AND UNCERTAINTY			
HAZARD CHARACTERIZATION ASPECT		**INPUTS**	**PROVISIONAL VALUE(S)**
PoD	LCL	237	Calculated from inputs
(Modelled BMD uncertainty)	UCL	535	Calculated from inputs
NOAEL to BMD	LCL	1	1
(NOAEL only)	UCL	1	1
Interspecies scaling	LCL	0.50	Case-specific
(Allometric for oral)	UCL	2.00	Case-specific
Interspecies TK/TD	LCL	0.333	0.333
(Remaining TK & TD)	UCL	3.00	3.00
Duration extrapolation	LCL	0.5	0.5
	UCL	8	8
Intraspecies	LCL	2.24	2.24
	UCL	41.88	41.88
Other aspect #1	LCL	1	1
(Description here)	UCL	1	1

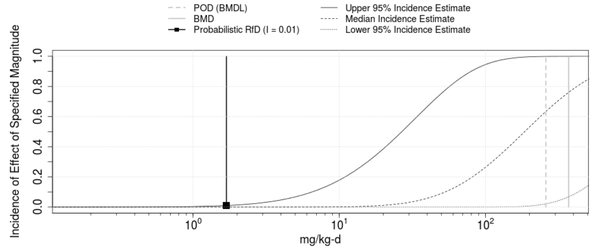
- Input on left entered by user
- Values on right are lower and upper confidence limits representing the estimated 5th and 95th percentiles of the lognormal distribution for the AFs.
  - LCL and UCL calculated using empirical data
- HDMI has lognormal distribution based on formula in Equation (1).

Example (cont'd)

APROBA output:

APPROXIMATE PROBABILISTIC ANALYSIS OUTPUTS			
Standard Confidence Interval			
Target Human Dose (HD_M^I)	**LCL (P05)**	**1.614**	**ppm**
	UCL (P95)	**209.390**	**ppm**
Degree of Uncertainty (Fold Range)			**129.8**
Estimated "Coverage" of Deterministic RfD			**91.7%**
Probabilistic RfD	= Approximate probabilistic HD_M^I at specified % confidence		
1.614	= Estimate of dose (ppm) at which, with confidence		
	95%		
	1%	of the population will have	**Absolute epididymal weight**
	of magnitude	≥	**10%**

RfV = 1.6 ppm, which is the LCL (P05 = 5th percentile) of the HDMI distribution.



Plot: CDFs of Lower, Median, and Upper Incidence Estimates

- Several types of "central" estimates can be derived, such as the median or the expected value, if assuming a log-normal distribution.
- The approach could also be modified to provide a distribution on the population risk at a given dose.
  - Distribution can be used to estimate benefits of reduced exposures or for communication about risks of exposure.

Next Steps

- Conduct a case study using APROBA to evaluate the advantages of incorporating quantitative uncertainty in assessments with this approach.
  - Evaluate the information and choices needed to produce the estimates.
  - Work with risk managers to evaluate if this approach is useful, and how it might need modification to be more useful.
- Apply uncertainty analysis to risk assessment done to support benefit-cost analysis.
- Non-APROBA-based uncertainty analysis.

References

- IPCS (International Programme on Chemical Safety). (2014). Guidance document on evaluating and expressing uncertainty in hazard characterization. World Health Organization.
- Chiu, WA; Slob, W. (2015). A unified probabilistic framework for dose–response assessment of human health effects. Environ Health Perspect (123) pp 1241-1254.
- Risk assessment and derivation of a provisional guideline value for melamine in drinking water. Advice to: Ministry of Infrastructure and Environment (Inspectorate of Environment and Transport) RIVM.

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