Abstract 1894
Poster Board 446

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Evaluating and Expressing Uncertainty in Dose-Response Assessment: A New WHO/IPCS Guidance Incorporating Probabilistic Approaches

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Abstract

Current practices in characterizing uncertainty and variability in human health hazards of chemicals include application of uncertainty factors, use of margins of exposure, and linear extrapolation from a point of departure. In order to advance more quantitative approaches to characterizing uncertainty and variability, the WHO/IPCS has developed a framework for evaluating and expressing uncertainty in dose-response assessment (known as "hazard characterization" in the WHO nomenclature). Consistent with the Adverse Outcome Pathway concept, this new framework for characterizing uncertainty makes a key conceptual distinction between (a) individual dose-response, in which the magnitude of effect (M) changes with dose, and (b) population dose-response due to inter-individual variability, in which the population incidence (I) at a particular magnitude of effect changes with dose. The framework also requires choices for M and I to be made explicit and transparent, unlike most traditional approaches, resulting in a single "unified" quantitative approach for assessing stochastic (cancer-like), deterministic (threshold-like), and continuous endpoints. Depending on the risk assessment needs as driven by the problem formulation, increasingly complex approaches may be employed to evaluate and express uncertainty, including the use of probabilistic methods. The presentation will focus on the fundamental concepts underlying the WHO/IPCS framework, the implementation of probabilistic approaches, and the interpretation of the resulting probabilistic dose-response assessments.

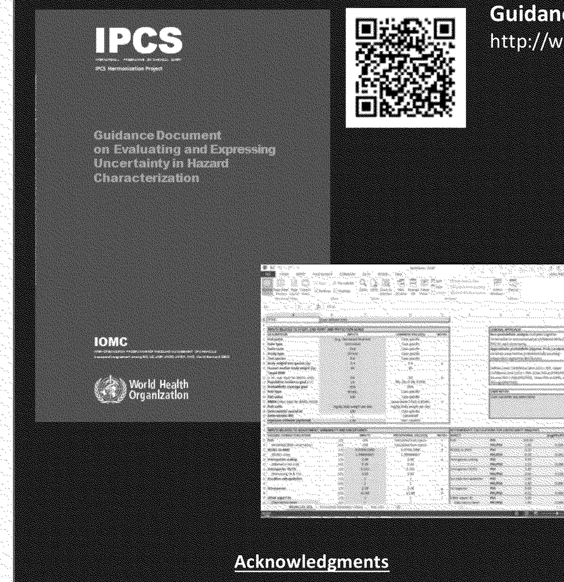
Purpose, Scope, and Context

Purpose:

Evaluating evaluating and expressing uncertainty in hazard characterization (=dose-response assessment)

Scope:

- Steps related to hazard identification (including evaluation of studies, endpoints, and mode of action) remain intact.
- Represents an extension of current approaches, not an alternative
- Maintains the same conceptual model of hazard characterization (dose-response assessment)
- Focuses on quantitative evaluation of uncertainties.



Guidance document and APROBA spreadsheet:
http://www.who.int/ipcs/methods/harmonization/areas/hazard_assessment/en/

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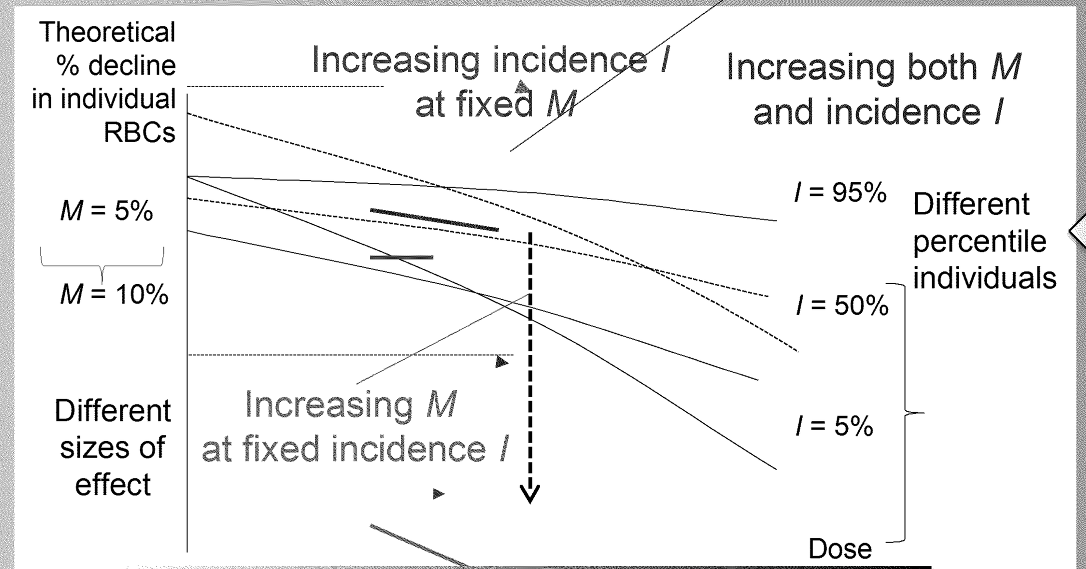


Key Concept: HD_M^I (e.g., HD_{10}^{05})

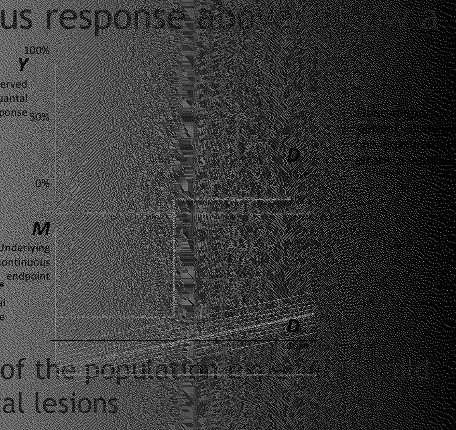
HD_M^I = the **human dose** at which a **fraction (or incidence) I of the population** shows an effect of **magnitude (or severity) M or greater** (for the critical effect considered).

- Magnitude of the effect M and the incidence in the population made explicit and transparent
- Choice of M and I are risk management "protection goals"

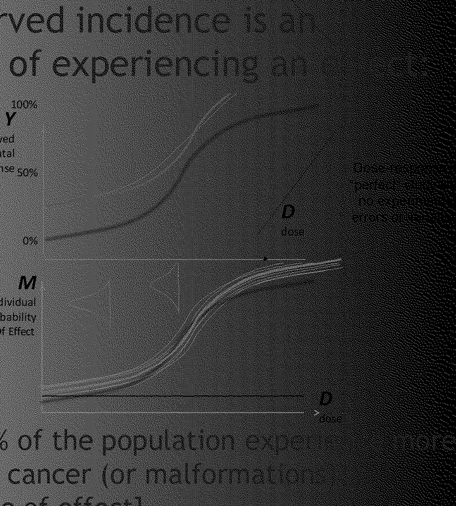
WHO/IPCS Uncertainty Framework Principles

1. Individual-level effects (magnitude=*M*) and population-level effects (incidence=*I*) are conceptually distinct
2. For all types of end-points, the magnitude of effect M can be regarded as changing gradually
3. The concept of an "effect metric" for M forms the basis of "equipotency" and differences in "sensitivity"
4. Making inferences from a point of departure involves making adjustments and accounting for variability and uncertainty

- **Continuous end points** already expressed as gradually changing
- **Deterministic quantal end points** = observed incidence is the fraction of individuals with a continuous response above/below a fixed cut-point:
  - Shape of the dose vs. incidence curve determined by experimental error and/or variability
  - Example: histopathological lesions
    - "M" is the severity score
    - "Y" is the fraction of severity ≥M*
    - HD_{mild}^{01} = human dose where 1% of the population experience mild (or more severe) histopathological lesions



- **Stochastic quantal end points** = observed incidence is an estimate of an individual's probability of experiencing an effect:
  - Shape of the dose vs. incidence curve largely determined by chemical and endpoint
  - Example: cancer, malformations
    - "M" is the individual probability of effect
    - "Y" is the fraction observed to experience the effect among homogeneous individuals
    - HD_{05}^{01} = human dose where at 1% of the population experience more than 5% individual probability of cancer (or malformations) [does NOT = population incidence of effect]



Conceptual Model

Test population (e.g., experimental animal)

↓ Inter-species **adjustment**

"Typical" member of target population (e.g., median human)

↓ Intra-species **variability**

"Sensitive" member of target population (e.g., 1st percentile human)

Traditional Deterministic Approach

Point of departure → Divide by inter-species factor → Divide by intra-species factor → Reference Dose

Limitations of Deterministic Approach

- If NOAEL, then *M* is unspecified and uncertainty is unquantified
- Factor assumed to be conservative, but unclear by how much
- Factor accounting for variability assumed to be conservative, but *I* is unspecified
- Assumed to be conservative, but unclear by how much
- More conservative with more factors (if +subchronic factor)
- Different assessments may differ greatly in level of conservatism
- Just providing a conservative bound not optimal for many types of decisions

WHO/IPCS Approach

Dose with effect size *M* in experimental animal

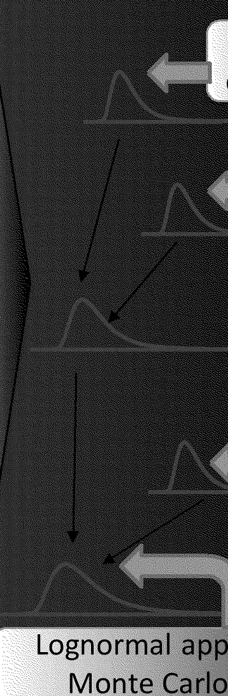
↓ Inter-species adjustment

Dose with effect size *M* in median human

↓ Ratio between median and *I*th percentile

Dose with effect size *M* in *I*th percentile human (HD_M^I)

Probabilistic Calculations



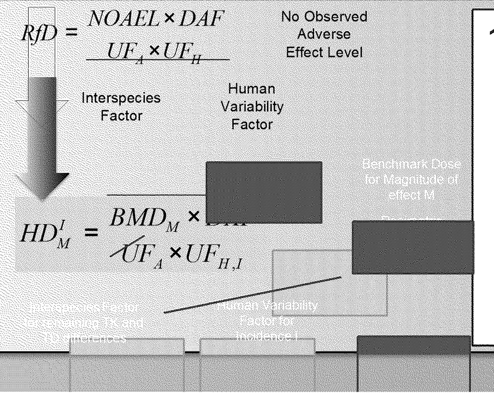
- Benchmark dose modeling
- Historical toxicity data across species
- Historical human data on variability and TK and/or TD
- Lognormal approximation or Monte Carlo simulation

"Effect metric" defines meaning of the same "M" across species or individuals.

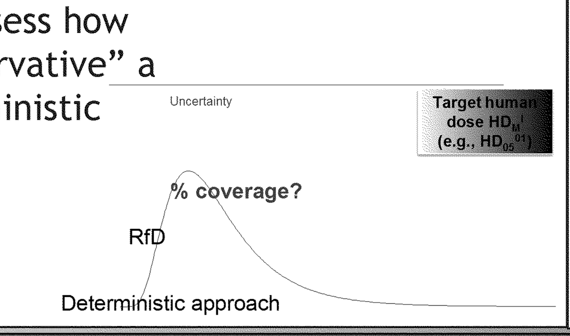
- Key issue is accounting for differences in background values
- Different approaches for different types of endpoints, such as

Endpoint type (examples)	M: Example toxicologically-equivalent effect metric.	*M**: Example critical effect size(s)	Benchmark dose approach
Continuous (hematocrit, serum enzyme, BW, organ/BW ratio)	Percent change relative to control	5%, 10% (percent change)	Continuous models with BMR= *M** = 5% , 10%.
Deterministic quantal (hepatic lesions, cytotoxicity)	Severity category	"Minimal," "Mild"	Quantal models for 50% incidence of *M** = Minimal, Mild
Stochastic quantal (hepatic tumors, fetal resorptions, eye malformations)	Extra risk for individual probability of occurrence	1%, 5%, 10% (extra risk)	Quantal models with BMR= *M** = 1%, 5%, 10%.

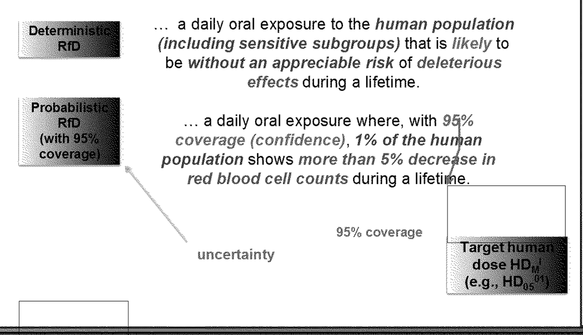
Why use HD_M^I?



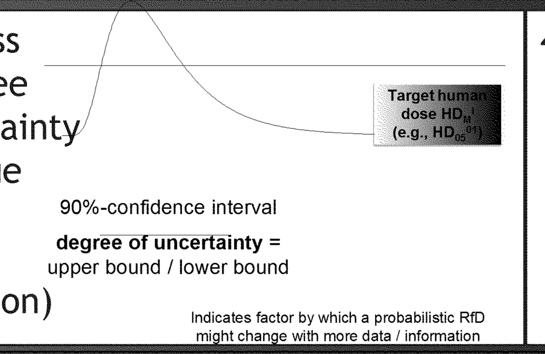
1. Can assess how "conservative" a deterministic RfD is



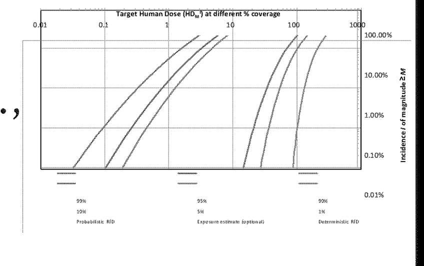
2. Can derive a "probabilistic RfD" with pre-specified coverage



3. Can assess the degree of uncertainty (and value of more data/ information)



4. Can derive dose-response *function* for all effects (e.g., to support socioeconomic analyses).



Practical Application

Key practical issues addressed in WHO/IPCS guidance:

Issue	WHO/IPCS Approach
Complex probabilistic calculations requiring Monte Carlo simulation.	Development of an accurate "approximate probabilistic approach" that can be implemented without Monte Carlo simulation.
Lack of user-friendly software.	Development of "APROBA" Excel® spreadsheet tool implementing the approximate probabilistic approach for rapid calculation of HD_M^I.
Need to specify input probability distributions.	Development of preliminary default distributions based on review of historical toxicity and human variability data, included in the APROBA spreadsheet tool.

APROBA Spreadsheet Tool

User provides:

- Study and endpoint data
  - Route and duration of exposure
  - Endpoint type (including if continuous, deterministic, or stochastic quantal)
  - Species and body weights
  - Results of benchmark dose calculations
- Risk management context/targets
  - Human body weight
  - Magnitude of effect *M* (=Benchmark response level, e.g., 5%)
  - Population incidence *I* (e.g., 1%)
  - Level of confidence (% coverage)

Spreadsheet automatically includes:

- Preliminary default input probability distributions for
  - NOAEL to BMD (if using NOAEL)
  - Interspecies scaling and TK/TD
  - Duration extrapolation
  - Intraspecies (human variability)
- Ability to modify distributions using
  - Chemical-specific data
  - Alternative default distributions

Spreadsheet automatically estimates (using approx. probabilistic approach):

- HD_M^I confidence limits
- Probabilistic reference dose
- Additional information
  - % contribution from different sources of uncertainty to overall uncertainty
  - Graphs of dose-response function (and confidence limits)

TITLE:	Example calculation	
INPUTS RELATED TO STUDY, END-POINT AND PROTECTION GOALS		
DESCRIPTION	**INPUTS**	**COMMON VALUE(S)**
End-point	Example calculation	Case-specific
Data type	Continuous	Case-specific
Data route	Oral	Case-specific
Study type	Chronic	Case-specific
Test species	Rat	Case-specific
Body weight test species (kg)	0.4	0.4
Human median body weight (kg)	60	60
Target BMR (= *M*, user input for BMDLs only)	5%	5%
Population incidence goal (= *I*)	1%	5%, 1%, 0.1%, 0.01%
Probabilistic coverage goal	95%	95%
PoD type	BMDL	Case-specific
PoD value	100	Case-specific
BMDU (User input for BMDL PoDs)	900	Case-specific
PoD units	mg/kg body weight per day	mg/kg body weight per day
Deterministic overall AF	100	Case-specific
Deterministic RfD	1	Calculated
Exposure estimate (optional)	1.00	User supplied

INPUTS RELATED TO ADJUSTMENT, VARIABILITY AND UNCERTAINTY			
HAZARD CHARACTERIZATION		**INPUTS**	**PROVISIONAL VALUE(S)**
PoD	LCL	100	Calculated from inputs
(Modelled BMD uncertainty)	UCL	900	Calculated from inputs
NOAEL to BMD	LCL	1	1
(NOAEL only)	UCL	1	1
Interspecies scaling	LCL	3.68	3.68
(Allometric for oral)	UCL	5.49	5.49
Interspecies TK/TD	LCL	0.333	0.333
(Remaining TK & TD)	UCL	3.00	3.00
Duration extrapolation	LCL	1	1
	UCL	1	1
Intraspecies	LCL	2.24	2.24
	UCL	41.88	41.88
Other aspect #1	LCL	1	1
(Description here)	UCL	1	1
Other aspect #2	LCL	1	1
(Description here)	UCL	1	1
Other aspect #3	LCL	1	1
(Description here)	UCL	1	1

NON-PROBABILISTIC ANALYSIS OUTPUTS			
Target Human Dose (HD_M^I)	LCL	0.1449	mg/kg body weight per day
	UCL	327.5900	mg/kg body weight per day
Fold Range of Uncertainty		2261.3	
Estimated "Coverage" of Non-Prob. LCL of HD_M^I*			99.8%
*Based on approximate probabilistic analysis, below.			

APPROXIMATE PROBABILISTIC ANALYSIS OUTPUTS			
Standard Confidence Interval			
Target Human Dose (HD_M^I)	LCL (P05)	0.807	mg/kg body weight per day
	UCL (P95)	58.803	mg/kg body weight per day
Degree of Uncertainty (Fold Range)			72.9
Estimated "Coverage" of Deterministic RfD			93.1%
Probabilistic RfD	= Approximate probabilistic HD_M^I at specified % confidence		
0.807	= Estimate of dose (mg/kg body weight per day) at which, with 95% confidence of the population will have 1% of magnitude ≥	Example calculation	5%

Implications for Risk Assessment, Risk Management, and Research

- Conceptual transition from deterministic toxicity values (e.g., RfD) to estimating a target human dose (HD_M^I) and its uncertainty
  - Similar to the transition from NOAEL to the BMD
  - Software such as WHO/IPCS Excel spreadsheet tool "APROBA" can facilitate uptake and use.
- Transparency as to risk management choices as to
  - "Protection goals" related to the "acceptable" magnitude of effect (M) and incidence (I) in the population, and
  - "Level of conservatism" related to percent confidence (given the uncertainties) that specified protection goals are met.
- Integration into a tiered approach by informing the question as to the value of additional analysis or data to reduce uncertainties.
- Incentive for further research to refine input probability distributions.

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