SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Contemporary Issues in Risk Assessment

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Harmonizing Dose-Response Assessment for Cancer and Non-Cancer Endpoints in Human Health Assessments

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Conflict of Interest Statement

I declare that neither I nor my family members have any financial interest with a commercial organization that has a direct or indirect interest in the subject matter of my presentation.

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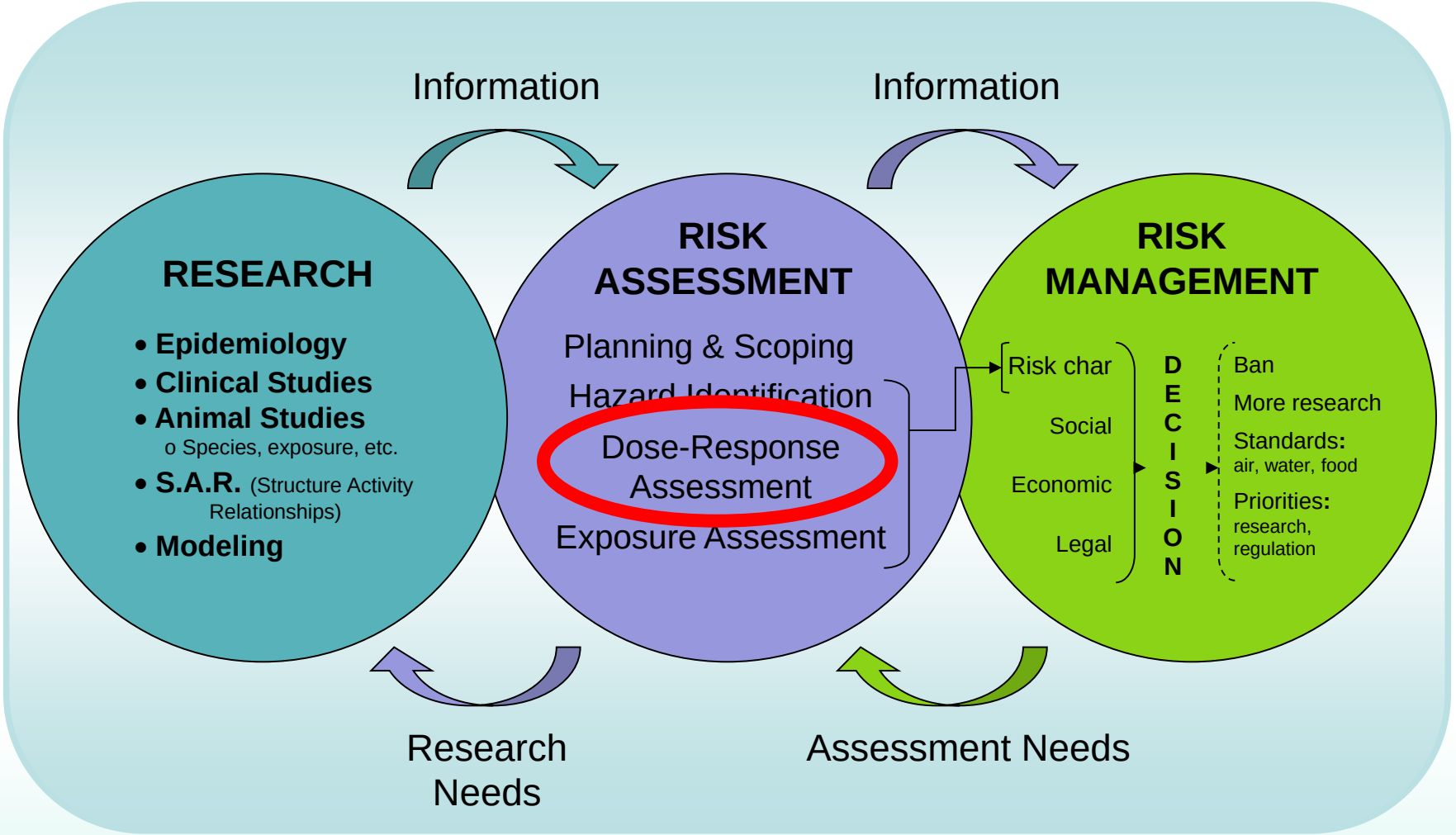
*Thanks for slides that have been adapted for this presentation. Additional slides have been adapted from EPA training courses.

Outline

- Current approaches to developing toxicity values
- WHO/IPCS framework for a new harmonized toxicity value: HD_M^I
- Demonstration of software tools to implement harmonized dose-response assessment
  - BMDS Wizard for dose-response modeling
  - APROBA for derivation of harmonized toxicity values
  - Case studies with deoxynivalenol and methyleugenol

Dose-Response Assessment in Context



Terminology

Adverse Effect

A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge.

Hazard Identification

Dose-Response Relationship

The relationship between a quantified exposure (dose) and the proportion of subjects demonstrating specific biologically significant changes in incidence and/or in degree of change (response).

Dose-Response Assessment

Toxicity Value

A numerical expression of a substance's exposure-response relationship that is used in risk assessments.

Point of Departure and Margin of Exposure

Identify studies and adverse effects
Evaluate mode of action (MOA)

↓

Identify or derive POD
(e.g., LOAEL, NOAEL, or BMDL)

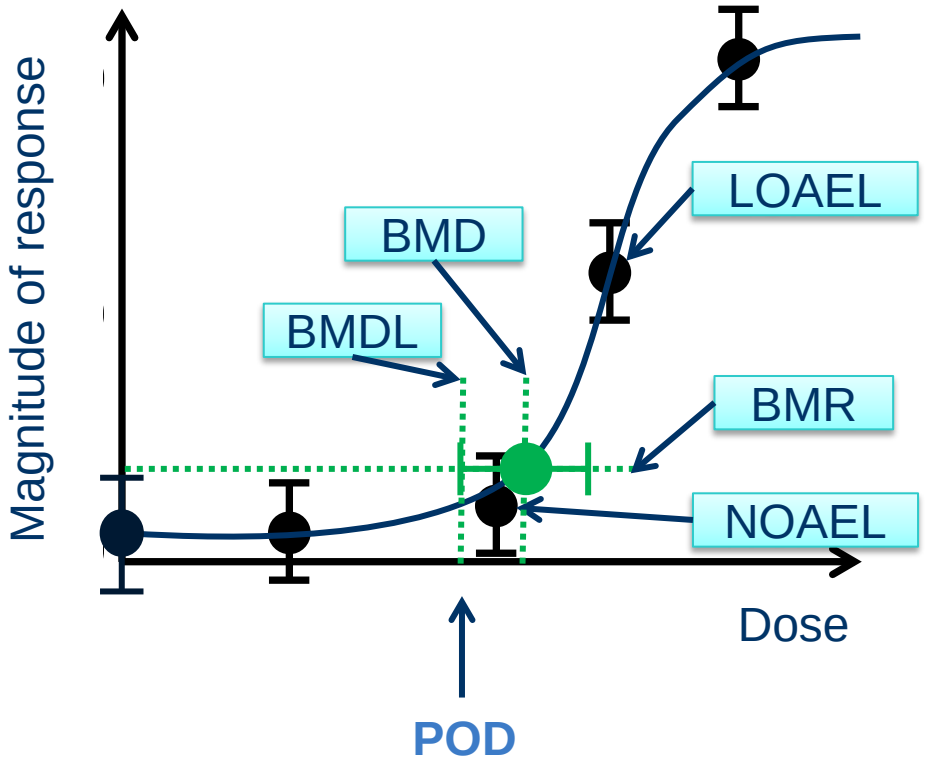
↓

Margin of Exposure (MOE):

$$\frac{\text{POD}}{\text{Exposure}}$$

Point of Departure (POD)

The dose-response point, derived from observed dose-response data, that marks the beginning of a low-dose extrapolation.



Reference Value and Hazard Quotient

Identify studies and adverse effects
Evaluate mode of action (MOA)

↓

Identify or derive POD
(e.g., LOAEL, NOAEL, or BMDL)

↓

Dosimetric Adjustment Factor (DAF)

↓

Select Uncertainty (or Chemical-Specific) Factors
- Interspecies (UF_A)
- Human variability (UF_H)
- Other (UF_{Other})

↓

Derive RfD or RfC:

$$\frac{POD \times DAF}{UF_A \times UF_H \times UF_{Other}}$$

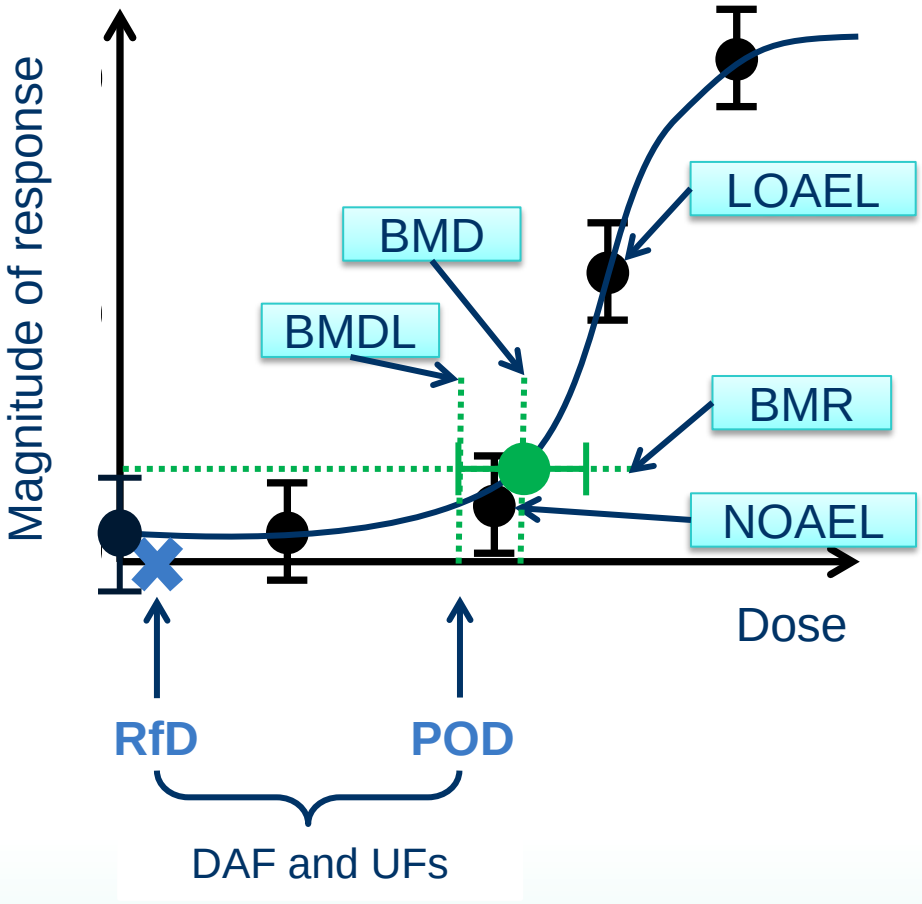
↓

Hazard Quotient (HQ):

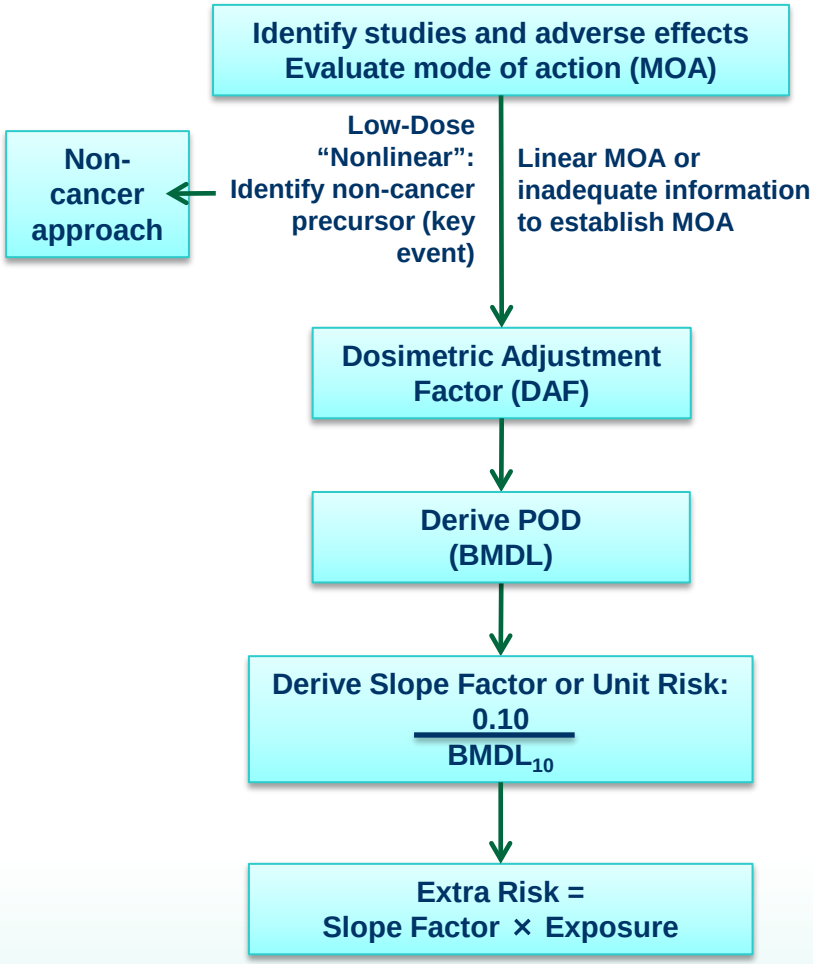
$$\frac{Exposure}{RfD}$$

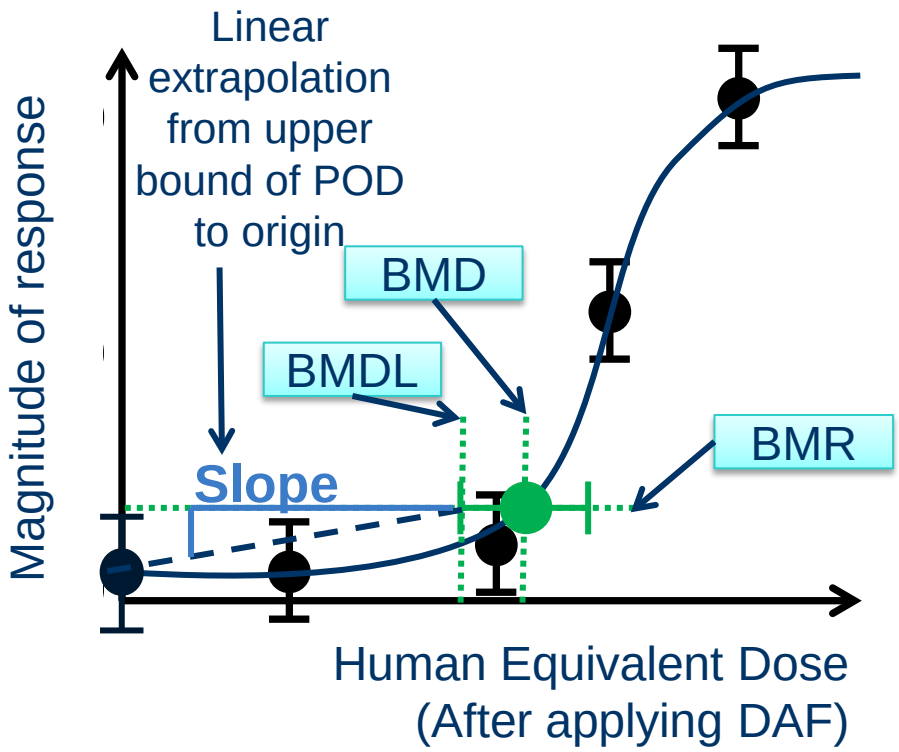
Reference Value (RfD or RfC)

An estimate of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime.



Slope Factor, Unit Risk, and Extra Risk





Unit Risk

The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m³ in air.

Summary of Typical Current Toxicity Values

Cancer or Noncancer Effects

Point of Departure (POD)

The dose-response point, derived from observed dose-response data, that marks the beginning of a low-dose extrapolation.

→ Margin of Exposure

Reference Value (RfD or RfC)

An estimate of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime.

→ Hazard Quotient

Cancer Effects

Slope Factor

An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent.

Unit Risk

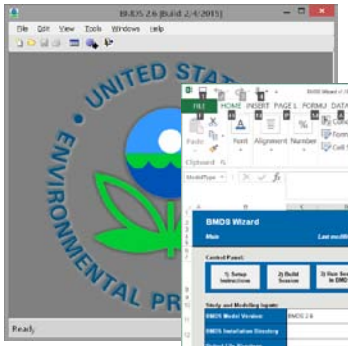
The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m³ in air.

→ Extra risk of Cancer

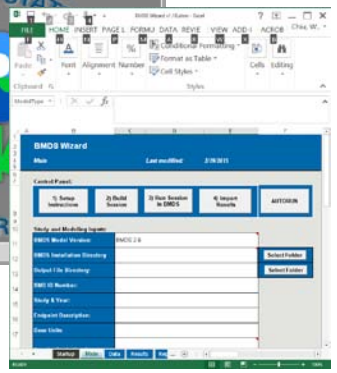
Partial progress towards harmonization

- Use of benchmark dose modeling

BMDS

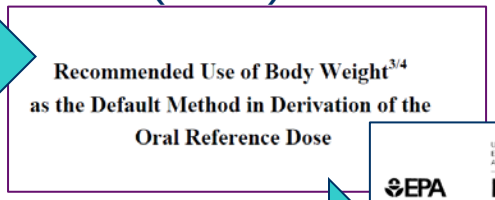


BMDS Wizard

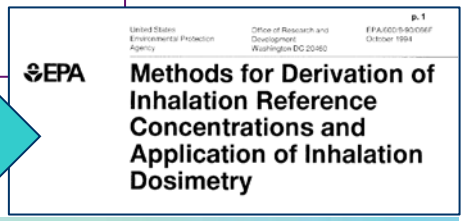


- Application of interspecies dosimetric adjustments
  - Allometric scaling

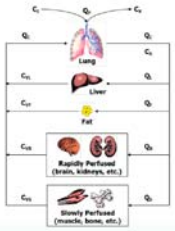
EPA (2011)

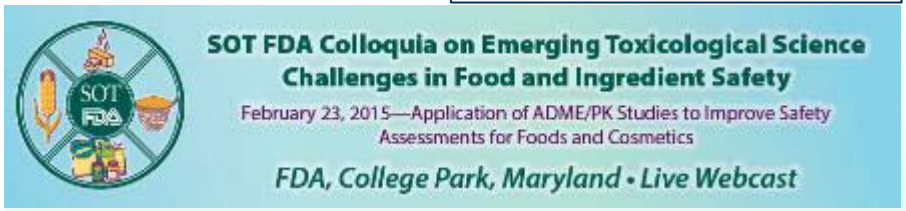


EPA (1994)

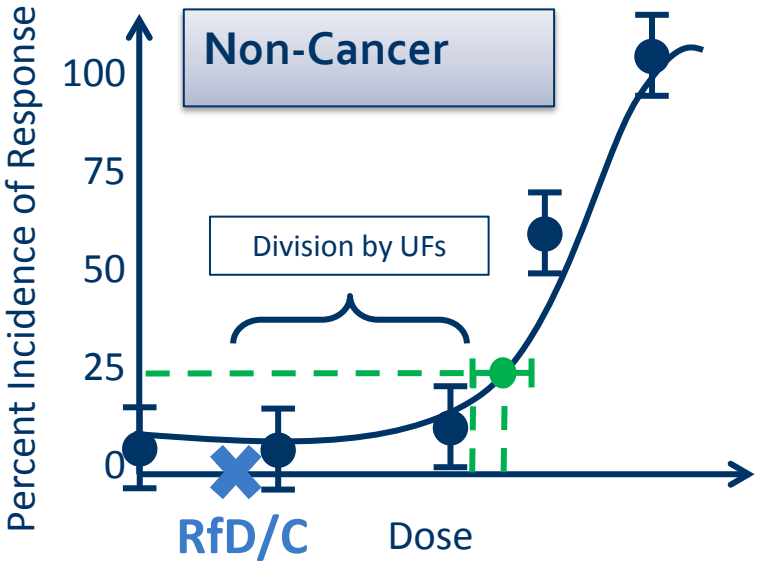


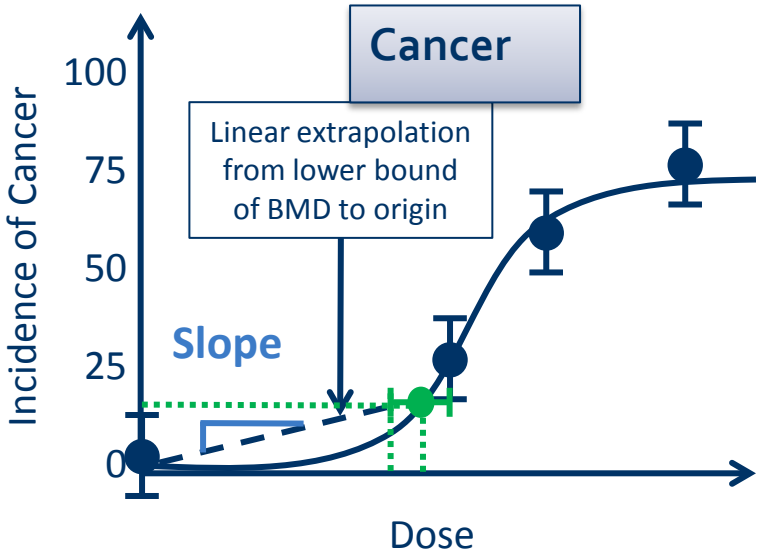
  - Inhalation dosimetry
  - PBPK modeling





Benchmark dose modeling





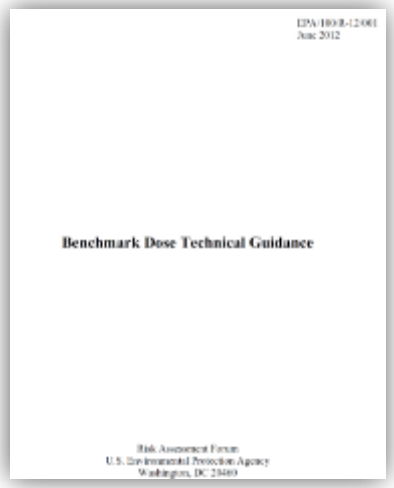
Benefits

- Uses all the data
- Independent of dose-spacing
- Transparent as to associated magnitude of response
- "Rewards" higher quality data

Challenges

- More complex, time-intensive
  - Software, guidance, training are available
- Not all data amenable
  - For non-cancer, can "fall-back" on NOAEL, LOAEL

Benchmark dose modeling resources (freely available)

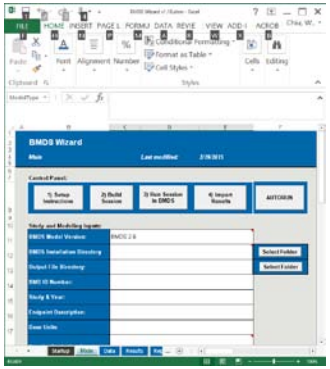

EPA/100R-12/001
June 2012

Benchmark Dose Technical Guidance

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

EPA Benchmark Dose Technical Guidance June 2012

EPA Benchmark Dose Software (BMDS) and online tutorials



ICF BMDS Wizard Excel Tool

RIVM PROAST R-package

All *EHP* content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307539.

Research

Standardizing Benchmark Dose Calculations to Improve Science-Based Decisions in Human Health Assessments

Jessica A. Wignall,[1] Andrew J. Shapiro,[1] Fred A. Wright,[2] Tracey J. Woodruff,[3] Weihsueh A. Chiu,[4] Kathryn Z. Guyton,[4] and Ivan Rusyn[1]

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Being incorporated into HAWC

HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

A content management system for human health assessments.

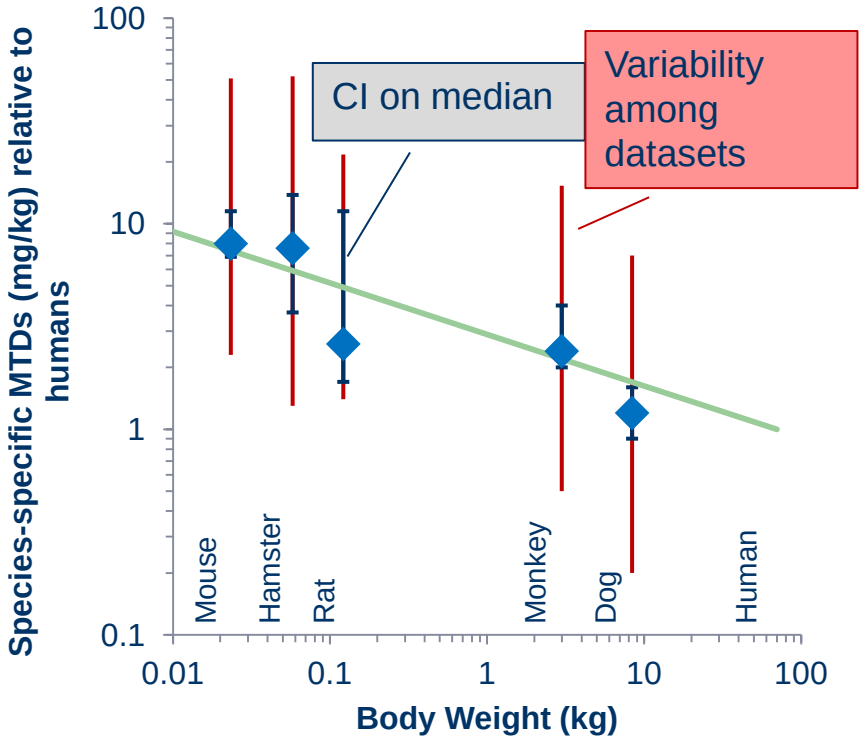
https://hawcproject.org/

Allometric scaling

- On “average,” species are equally sensitive after adjusting for body size.

  $DAF = (BW_{animal}/BW_{human})^{1-\alpha}$

  $\alpha \approx 0.7$ or 0.75



- Now applied to both cancer and non-cancer assessments.
- Non-cancer assessments also address the substantial chemical-to-chemical variability due to chemical-specific toxicokinetics and toxicodynamics.

Outline

- Current approaches to developing toxicity values
- **WHO/IPCS framework for a new harmonized toxicity value: HD_M^I**
- Demonstration of software tools to implement harmonized dose-response assessment
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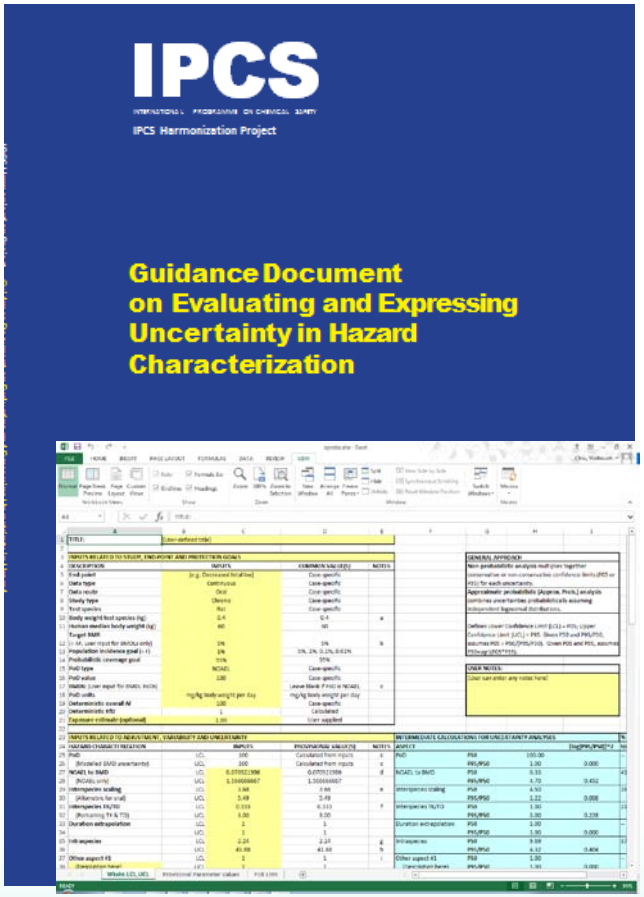
Key missing harmonization elements addressed by WHO/IPCS

- Non-cancer (and non-linear cancer) assessments are missing
  - Quantitative risk estimates (e.g., incidence)
  - Distinction between uncertainty from variability
- Cancer assessments are missing
  - Explicit accounting of human variability
  - Incorporation of interspecies (or other) uncertainties
- Both types of assessments
  - Output a single point estimate
  - Assumed to be “conservative” but unclear by how much

Harmonization Project Document No. 11



APROBA spreadsheet tool

Limitations addressed by WHO/IPCS with a "unified" toxicity value: HD_M^I

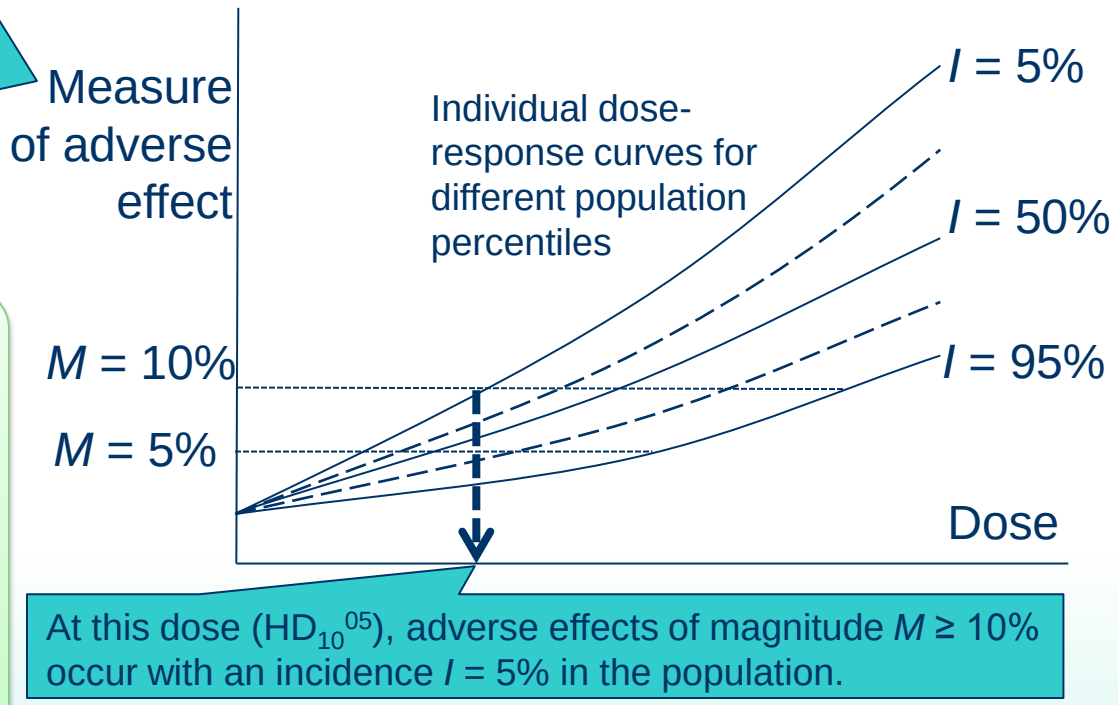
HD_M^I = the **human dose** at which a **fraction (or incidence) *I* of the population** shows an effect of **magnitude (or severity) *M* or greater** for the adverse effect considered.

Effect measures

- Percent change (e.g., 5%, 10%)
- Lesion severity (e.g., mild, moderate)
- Extra risk for individual probability of effect (e.g., 1%, 10% extra risk of cancer)

Benefits to harmonization:

- Provides quantitative risk estimate in terms of incidence.
- Addresses interspecies and other uncertainties.
- Separately addresses variability.
- Probabilistic analysis can provide uncertainty distribution or confidence interval.



Adapted from WHO/IPCS *Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization* (WHO 2014)

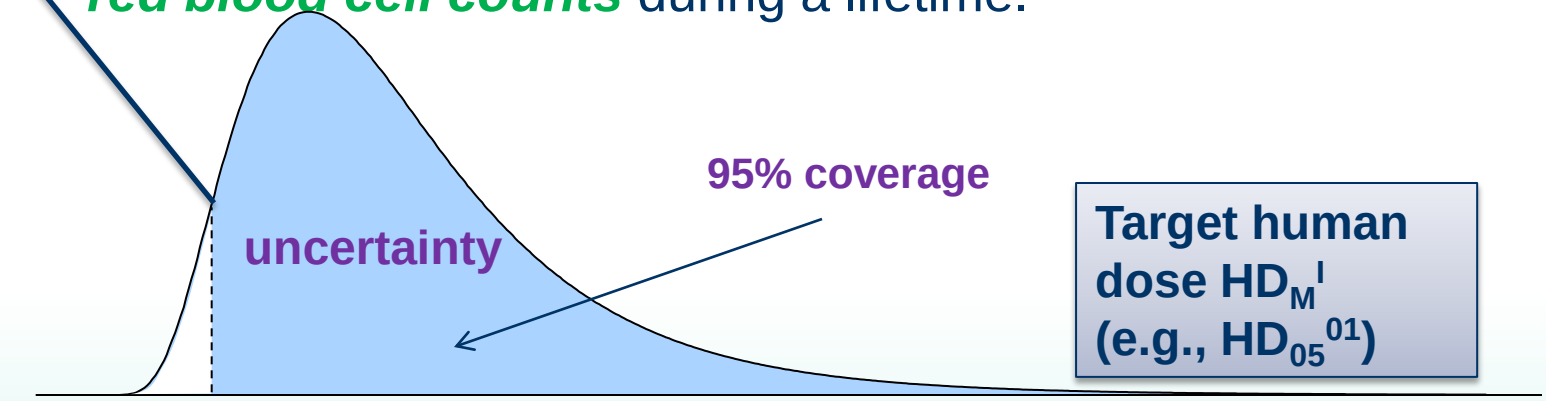
Refining the definition of the RfD in terms of the HD_M^I

Deterministic RfD

… a daily oral exposure to the ***human population (including sensitive subgroups)*** that is ***likely*** to be ***without an appreciable risk*** of ***deleterious effects*** during a lifetime.

Probabilistic RfD (with 95% coverage)

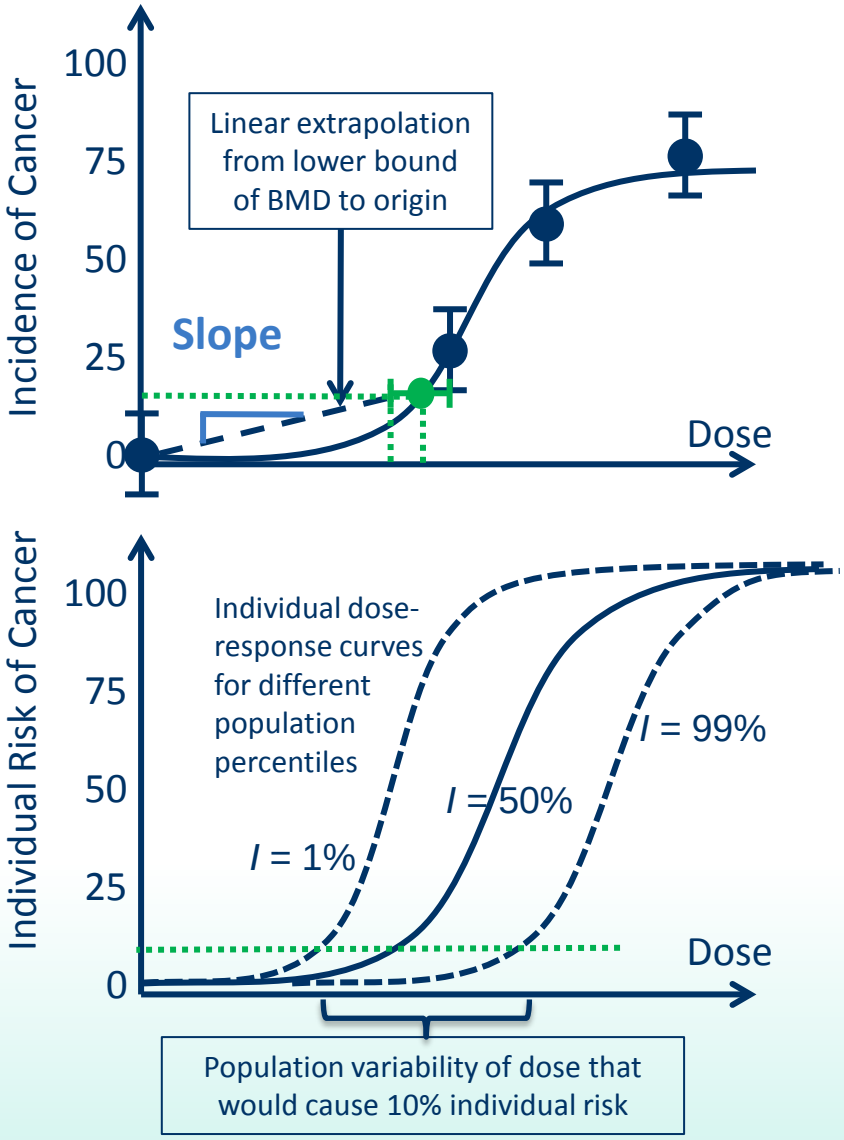
… a daily oral exposure where, with ***95% coverage (confidence)***, ***1% of the human population*** shows ***more than 5% decrease in red blood cell counts*** during a lifetime.



Adapted from WHO (2014)

HD_M^I implies a re-orientation of cancer assessment

- Current cancer assessments use linear extrapolation to estimate population incidence (assumes everyone has same slope).
- In the harmonized approach, cancer assessments are re-oriented to estimating
  - Individual risk of cancer, and
  - The variation of individual risk across the population.
- Population incidence can still be calculated by integrating individual risk over the population.



HD_M^I derived using a unified approach for cancer and non-cancer effects

Conceptual Model

Step 1. Dose that will cause effect of magnitude *M** in the experimental animal.

Interspecies, study-specific adjustments

Step 2. Dose that will cause effect of magnitude *M** in the median human.

Accounting for human variability

Step 3. Dose that will cause effects of magnitude ≥*M** with incidence *I** in the human population.

Adapted from WHO (2014), Chiu and Slob (2015)

Unified Approach

Identify studies and adverse effects
Evaluate mode of action (MOA)

↓

Derive POD_{M^*} associated with effect of magnitude *M** (e.g., BMD_{M^*})

↓

Dosimetric Adjustment Factor (DAF)

↓

Factors Addressing Uncertainty: Interspecies (UF_A) and Other (UF_{Other})

↓

Human Variability Factor For Incidence *I** (HV_{I^*})

↓

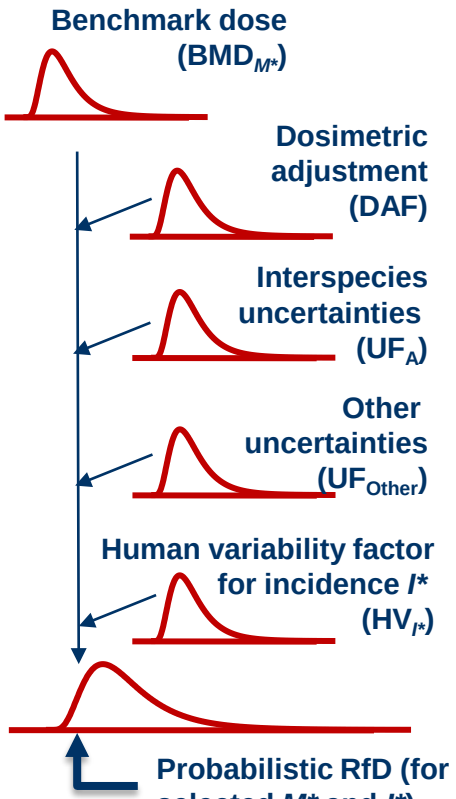
Derive $HD_{M^*}^{I^*}$:

$$\frac{BMD_{M^*} \times DAF \times HV_{I^*}}{UF_A \times UF_{Other}}$$

↓

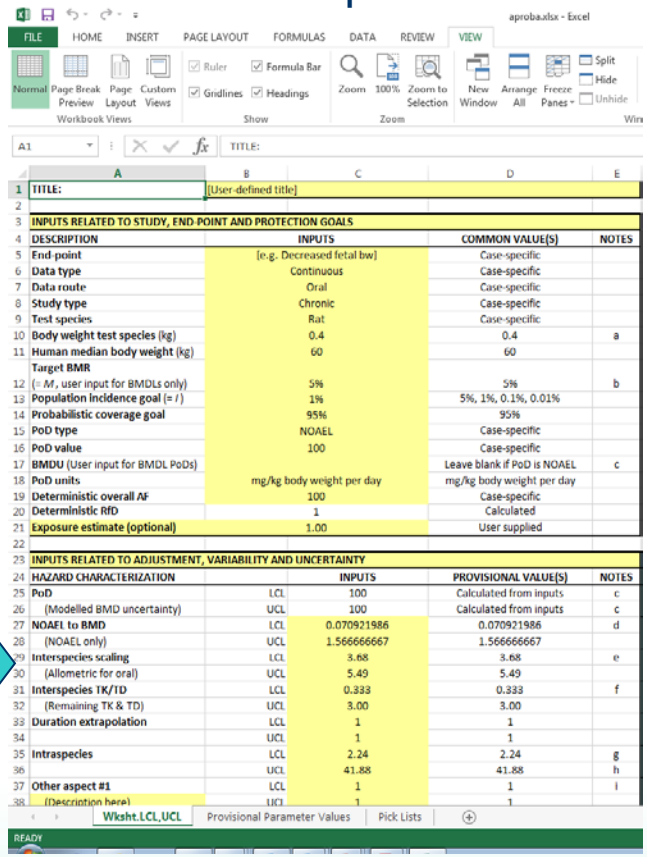
Individual Margin of Exposure | **Probabilistic RfD** | Incidence of Effects

Probabilistic Analysis



Harmonization and data integration facilitated by “APROBA” Excel tool

“APROBA” Spreadsheet

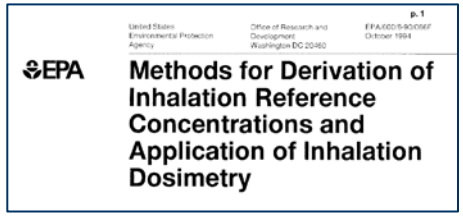


	A	B	C	D	E
1	TITLE:	[User-defined title]			
2					
3	INPUTS RELATED TO STUDY, END-POINT AND PROTECTION GOALS				
4	DESCRIPTION		INPUTS	COMMON VALUE(S)	NOTES
5	End-point		[e.g. Decreased fetal bw]	Case-specific	
6	Data type		Continuous	Case-specific	
7	Data route		Oral	Case-specific	
8	Study type		Chronic	Case-specific	
9	Test species		Rat	Case-specific	
10	Body weight test species (kg)		0.4	0.4	a
11	Human median body weight (kg)		60	60	
	Target BMR				
12	(= M, user input for BMDLs only)		5%	5%	b
13	Population incidence goal (= I)		1%	5%, 1%, 0.1%, 0.01%	
14	Probabilistic coverage goal		95%	95%	
15	PoD type		NOAEL	Case-specific	
16	PoD value		100	Case-specific	
17	BMDU (User input for BMDL PoDs)			Leave blank if PoD is NOAEL	c
18	PoD units		mg/kg body weight per day	mg/kg body weight per day	
19	Deterministic overall AF		100	Case-specific	
20	Deterministic RfD		1	Calculated	
21	Exposure estimate (optional)		1.00	User supplied	
22					
23	INPUTS RELATED TO ADJUSTMENT, VARIABILITY AND UNCERTAINTY				
24	HAZARD CHARACTERIZATION		INPUTS	PROVISIONAL VALUE(S)	NOTES
25	PoD	LCL	100	Calculated from inputs	c
26	(Modelled BMD uncertainty)	UCL	100	Calculated from inputs	c
27	NOAEL to BMD	LCL	0.070921986	0.070921986	d
28	(NOAEL only)	UCL	1.566666667	1.566666667	
29	Interspecies scaling	LCL	3.68	3.68	e
30	(Allometric for oral)	UCL	5.49	5.49	
31	Interspecies TK/TD	LCL	0.333	0.333	f
32	(Remaining TK & TD)	UCL	3.00	3.00	
33	Duration extrapolation	LCL	1	1	
34		UCL	1	1	
35	Intraspecies	LCL	2.24	2.24	g
36		UCL	41.88	41.88	h
37	Other aspect #1	LCL	1	1	i
38	(Description here)	UCL	1	1	

Wksht.LCL,UCL | Provisional Parameter Values | Pick Lists

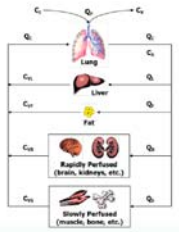
READY

Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose



EPA

Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry



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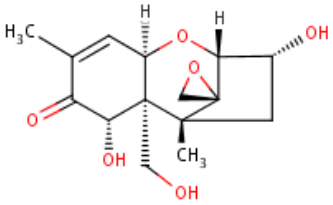
Two case studies: Use of BMDS Wizard and APROBA to derive HD_M^I

Non-cancer: Deoxynivalenol

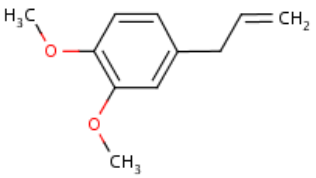


Source: TOXNET/ChemID plus

- Mycotoxin in cereals ("vomitoxin")
- Highly prevalent in food with widespread exposure

- Adverse noncancer effects:
  - Decreased body weight
  - Prenatal development
  - Male fertility

Cancer: Methyleugenol



- Natural component of essential oils
- Used as flavoring agent, fragrance, insect attractant

- IARC Group 2B (possibly carcinogenic)
  - Liver tumors in rats and mice
  - Multiple other tumors in rats

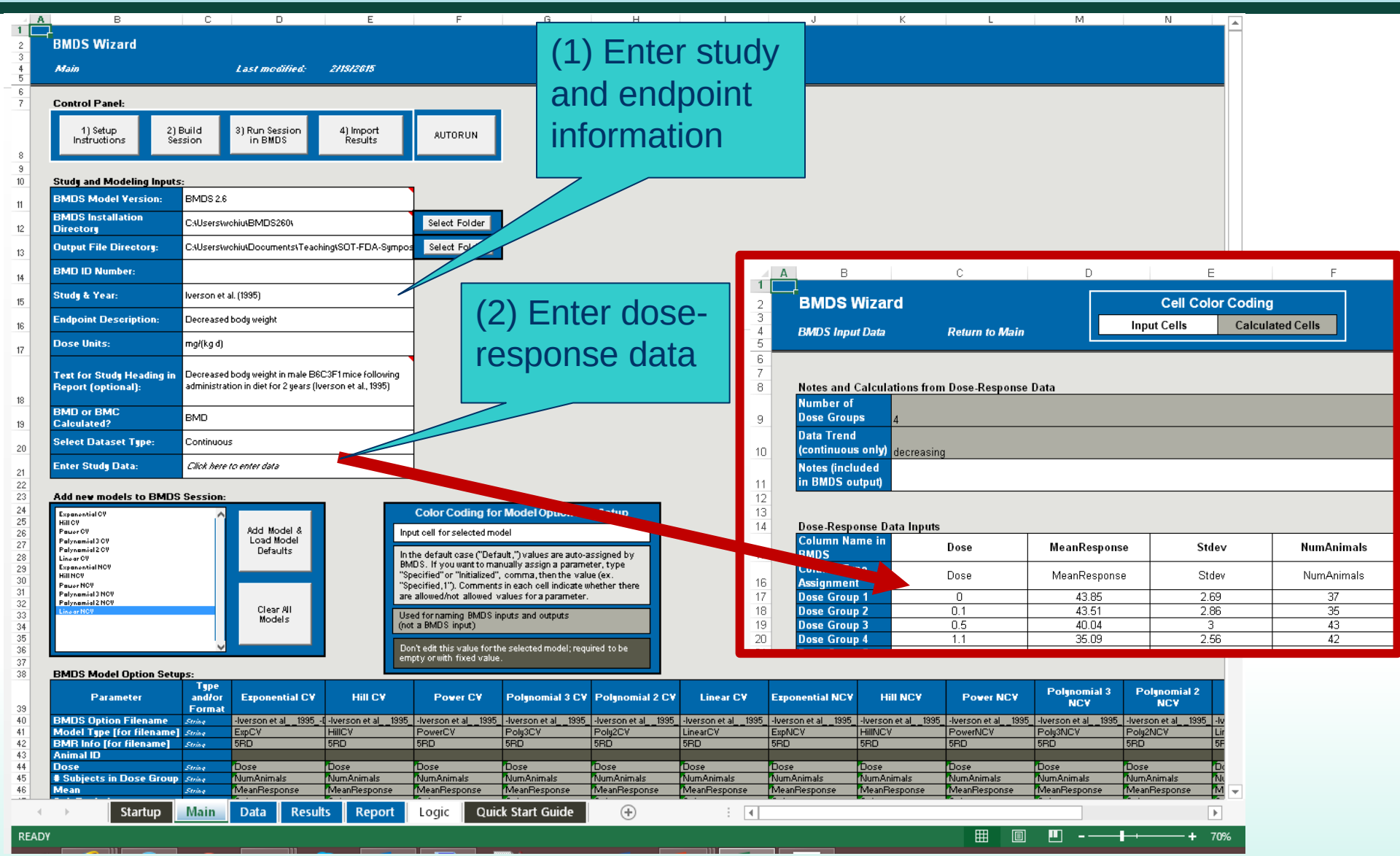
How do you calculate the HD_M^I?

1. **Select "*M*" and "*I*"**
   - **DON: *M*=5% change in body weight; I=1% incidence**
   - **MET: M=1% or 10% extra risk; I=1% incidence**
2. Use BMDS Wizard to estimate BMD
   - Model selection: Lowest AIC (can evaluate other models in sensitivity analysis)
   - Upper confidence limit ≈ BMD * (BMD/BMDL)
3. Use APROBA to estimate HD_M^I
   - Probabilistic RfD = lower 95% confidence limit on HD_M^I
   - What is the range of uncertainty?
   - How does HD_M^I change with incidence?
4. Characterizing uncertainty
   - What are the largest sources of uncertainty?
   - What are options for additional data generation/analysis?

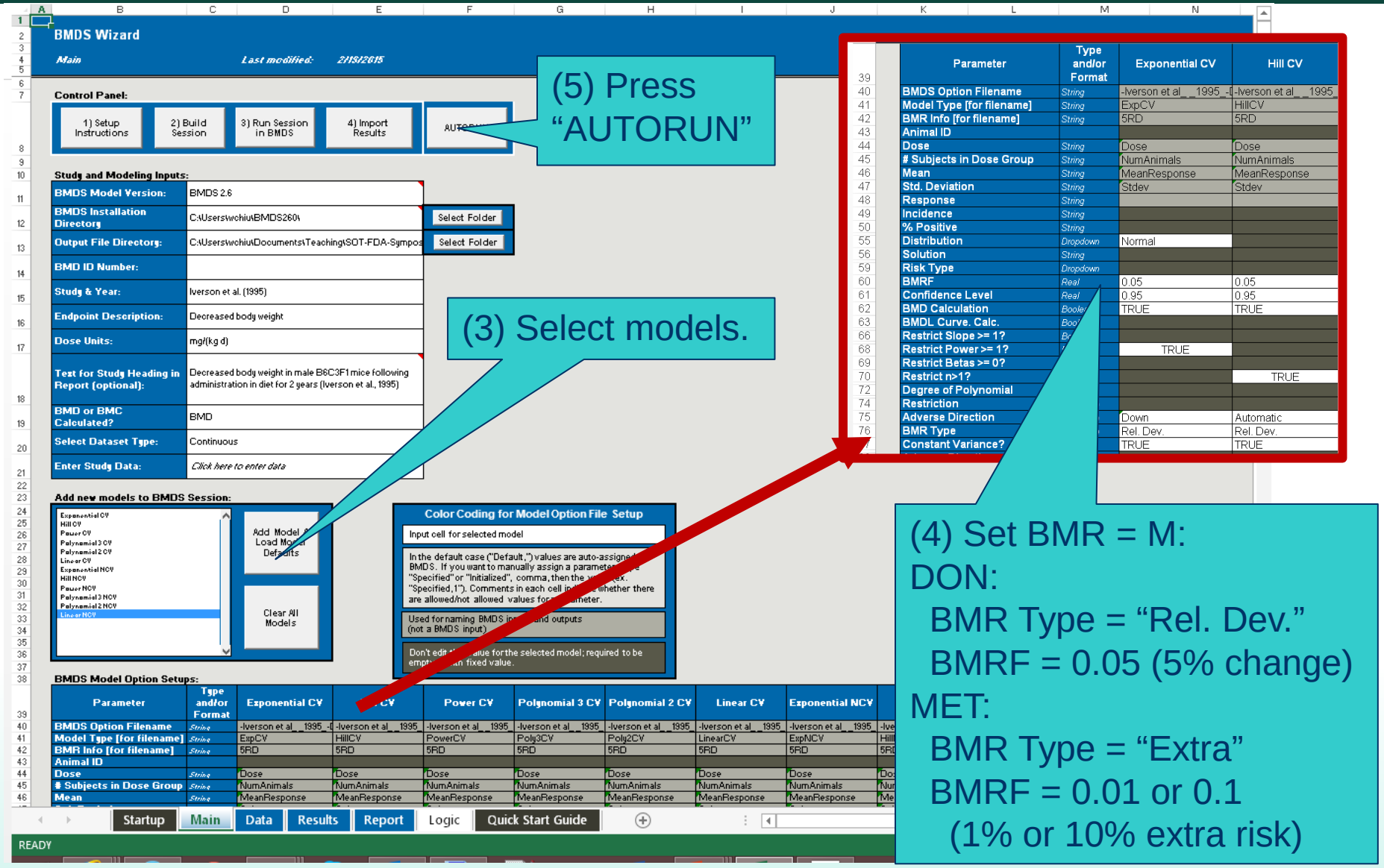
BMDS Wizard

- Microsoft Excel-based tool developed by ICF International (no cost to users) that streamlines use of U.S. EPA's BMDS for modeling dose-response data:
  - Data entry
  - Modeling option selection
  - Running multiple models
  - Decision logic for selecting models
- Similar functionality being developed in HAWC to provide "one-stop shop" from literature search to dose-response.
- Alternative: Use RIVM's "PROAST" R-package

BMDS Wizard Inputs



BMDS Wizard Inputs



(5) Press "AUTORUN"

(3) Select models.

Parameter	Type and/or Format	Exponential CV	Hill CV
BMDS Option Filename	String	-Iverson et al__1995_	-Iverson et al__1995_
Model Type [for filename]	String	ExpCV	HillCV
BMR Info [for filename]	String	5RD	5RD
Animal ID			
Dose	String	Dose	Dose
# Subjects in Dose Group	String	NumAnimals	NumAnimals
Mean	String	MeanResponse	MeanResponse
Std. Deviation	String	Stdev	Stdev
Response	String		
Incidence	String		
% Positive	String		
Distribution	Dropdown	Normal	
Solution	String		
Risk Type	Dropdown		
BMRF	Real	0.05	0.05
Confidence Level	Real	0.95	0.95
BMD Calculation	Boolean	TRUE	TRUE
BMDL Curve. Calc.	Boo		
Restrict Slope >= 1?	Bo		
Restrict Power >= 1?		TRUE	
Restrict Betas >= 0?			
Restrict n>1?			TRUE
Degree of Polynomial			
Restriction			
Adverse Direction		Down	Automatic
BMR Type		Rel. Dev.	Rel. Dev.
Constant Variance?		TRUE	TRUE

(4) Set BMR = M:

DON:

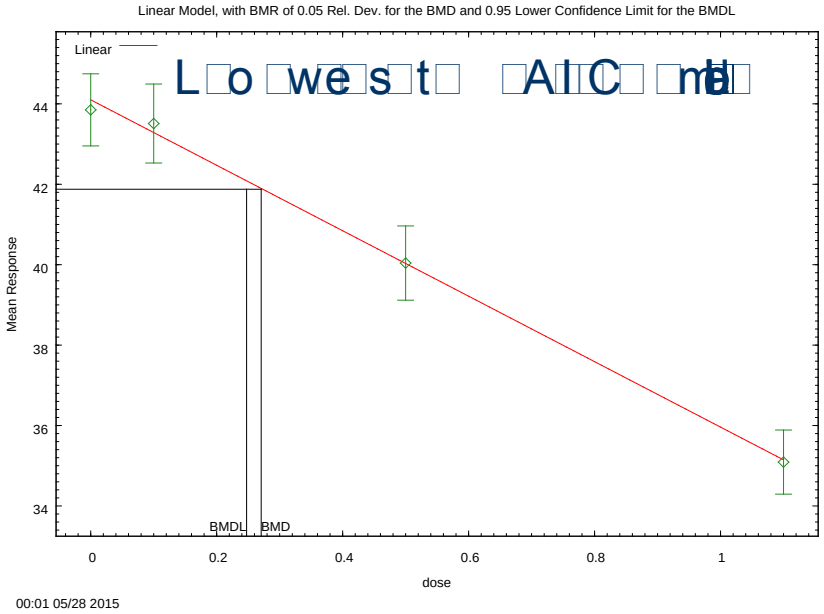
- BMR Type = "Rel. Dev."
- BMRF = 0.05 (5% change)

MET:

- BMR Type = "Extra"
- BMRF = 0.01 or 0.1 (1% or 10% extra risk)

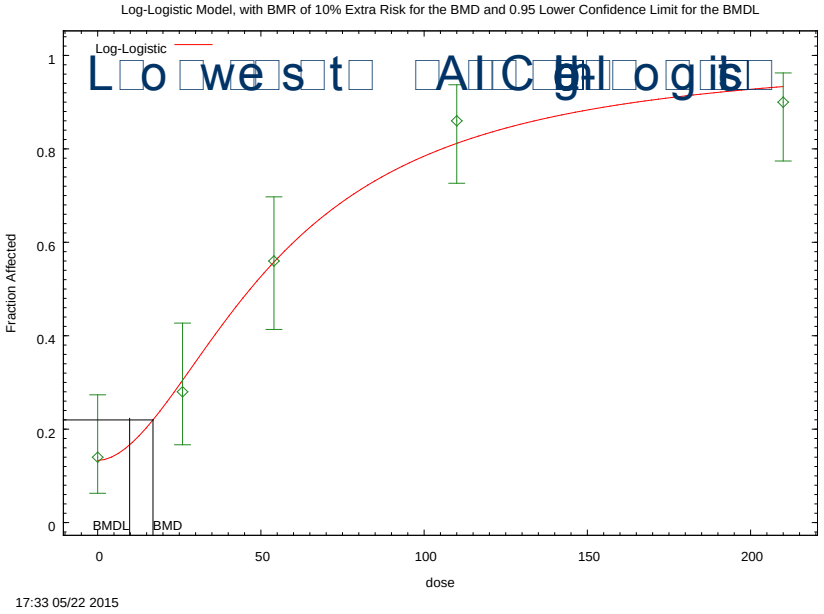
BMDS Wizard Results

Deoxynivalenol



BMR =5% relative deviation
BMDL = 0.248 (95% CI)
BMDU = 0.296 (95% CI)

Methyleugenol



BMR= 10% extra risk
BMDL = 9.80 (95% CI)
BMDU = 29.1 (95% CI)

*BMR = 1% extra risk
BMDL = 1.75 (95% CI)
BMDU = 12.5 (95% CI)

How do you calculate the HD_M^I?

1. **Select "*M*" and "*I*"**
   - **DON: *M*=5% change in body weight; I=1% incidence**
   - **MET: M=1% or 10% extra risk; I=1% incidence**
2. **Use BMDS Wizard to estimate BMD**
   - **Model selection: Lowest AIC (can evaluate other models in sensitivity analysis)**
   - **Upper confidence limit ≈ BMD * (BMD/BMDL)**
3. Use APROBA to estimate HD_M^I
   - Probabilistic RfD = lower 95% confidence limit on HD_M^I
   - What is the range of uncertainty?
   - How does HD_M^I change with incidence?
4. Characterizing uncertainty
   - What are the largest sources of uncertainty?
   - What are options for additional data generation/analysis?

APROBA

- Microsoft Excel-based tool developed by WHO/IPCS Workgroup that conducts “approximate” probabilistic dose-response analysis:
  - Framework for calculating HD_M^I
  - Preliminary default distributions included (modifiable by user)
- Training course being developed (given for the first time at Eurotox in September 2015).
- Next version to incorporate probabilistic exposure assessment.

APROBA Tool: General Layout

Input Section

Contributions to Uncertainty Section

Approximate Probabilistic Output Section

APROBA Inputs

	INPUTS RELATED TO STUDY, END-POINT AND PROTECTION GOALS		
4	**DESCRIPTION**	**INPUTS**	**COMMON V**
5	**End-point**	Decreased Body Weight	Case-spe
6	**Data type**	Continuous	Case-spe
7	**Data route**	Oral	Case-spec
8	**Study type**	Chronic	Case-specific
9	**Test species**	Mouse	Case-specific
10	**Body weight test species** (kg)	0.04385	0.0
11	**Human median body weight** (kg)	70	60
12	**Target BMR** (= *M* , user input for BMDLs only)	5%	5%
13	**Population incidence goal** (= *I*)	1%	5%, 1%, 0.1
14	**Probabilistic coverage goal**	95%	95%
15	**PoD type**	BMDL	Case-specific
16	**PoD value**	0.248	Case-specif
17	**BMDU** (User input for BMDL PoDs)	0.296	Case-specif
18	**PoD units**	mg/kg body weight per day	mg/kg body weigh
19	**Deterministic overall AF**	100	Case-specif
20	**Deterministic RfD**	0.00248	Calculated
21	**Exposure estimate (optional)**		User supplie

Study- and endpoint-specific information

Risk management protection goals

BMDS Wizard Results

APROBA Inputs

23	**INPUTS RELATED TO ADJUSTMENT, VARIABILITY AND UNCERTAINTY**			
24	**HAZARD CHARACTERIZATION**		**INPUTS**	**PROVISIO**
25	**PoD**	LCL	0.248	Calculate
26	(Modelled BMD uncertainty)	UCL	0.296	Calculate
27	**NOAEL to BMD**	LCL	1	
28	(NOAEL only)	UCL	1	
29	**Interspecies scaling**	LCL	6.80	
30	(Allometric for oral)	UCL	12.28	
31	**Interspecies TK/TD**	LCL	0.333	
32	(Remaining TK & TD)	UCL	3.00	
33	**Duration extrapolation**	LCL	1	
34		UCL	1	
35	**Intraspecies**	LCL	2.24	2.24
36		UCL	41.88	41.88
37	**Other aspect #1**	LCL	1	1
38	(Description here)	UCL	1	1
39	**Other aspect #2**	LCL	1	1
40	(Description here)	UCL	1	1
41	**Other aspect #3**	LCL	1	1
42	(Description here)	UCL	1	1

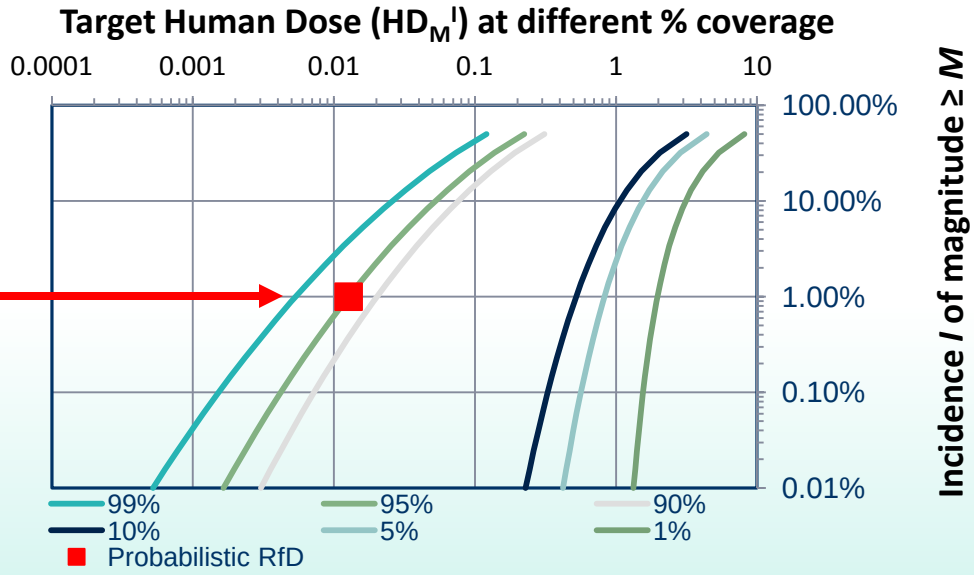
Preliminary default distributions calculated based on WHO/IPCS review/ analysis (editable)

APROBA Calculation of HD_M^I and Probabilistic RfD

51	APPROXIMATE PROBABILISTIC ANALYSIS OUTPUTS			
52	Standard Confidence Interval			
53	Target Human Dose (HD_M^I)	LCL (P05)	0.00048	mg/kg body weight per day
54		UCL (P95)	0.020	mg/kg body weight per day
55	Degree of Uncertainty (Fold Range)			41.0
56	Estimated "Coverage" of Deterministic RfD			57.4%
57	Probabilistic RfD	= Approximate probabilistic HD_M^I at specified % confidence		
58	0.00048	= Estimate of dose (mg/kg body weight per day) at which, with		
59		95%	confidence	
60		1%	of the population will have	Decreased Body Weight
61		of magnitude	≥	5%

HD_M^I confidence interval

Probabilistic Reference Dose



APROBA Results

Deoxynivalenol

- **Probabilistic RfD:** At 0.00048 mg/(kg d) exposure, there is 95% confidence that only 1% of the population will experience 5% (or more) body weight reduction
- 41-fold uncertainty (90% two-tailed confidence interval)

Methyleugenol

- **Probabilistic RfD:** At 0.054 mg/(kg d) exposure, there is 95% confidence that only 1% of the population will experience an extra risk of cancer of 10% (or more)
- 47-fold uncertainty (90% two-tailed confidence interval)
- For extra risk of 1%
  - Prob. RfD=0.013 mg/(kg d)
  - 65-fold uncertainty

Note: Calculating overall population incidence of cancer requires separate Monte Carlo simulation (beyond the scope of this presentation). See Chiu and Slob (2015).

How do you calculate the HD_M^I?

1. **Select "*M*" and "*I*"**
   - **DON: *M*=5% change in body weight; I=1% incidence**
   - **MET: M=1% or 10% extra risk; I=1% incidence**
2. **Use BMDS Wizard to estimate BMD**
   - **Model selection: Lowest AIC (can evaluate other models in sensitivity analysis)**
   - **Upper confidence limit ≈ BMD * (BMD/BMDL)**
3. **Use APROBA to estimate HD_M^I**
   - **Probabilistic RfD = lower 95% confidence limit on HD_M^I**
   - **What is the range of uncertainty?**
   - **How does HD_M^I change with incidence?**
4. Characterizing uncertainty
   - What are the largest sources of uncertainty?
   - What are options for additional data generation/analysis?

Contributions to uncertainty and options for reducing it

Percent Contribution to Uncertainty (Variance)	DON	MET (BMR=10%)	MET (BMR=1%)
POD (BMD)	<1%	8%	22%
Dosimetry	3%	1%	1%
Interspecies	35%	33%	28%
Human Variability	62%	58%	49%
Overall Uncertainty	**41-fold**	**47-fold**	**65-fold**

Better dose-response data (greater "n")

PBPK models in rodents and humans

Toxicodynamic studies (in vivo or in vitro)

Numerous emerging data streams

Population-based models and experimental in vivo and in vitro data*

* See NIEHS "Population-Based Rodent Resources for Environmental Health Sciences Meeting" http://www.niehs.nih.gov/about/visiting/events/pastmtg/2015/rodent_resources/index.cfm

Conclusions: Harmonization of cancer and non-cancer dose-response assessment

- Limited harmonization in current approaches to developing toxicity values
  - Benchmark dose modeling to estimate point of departure
  - Allometric scaling to adjust for interspecies differences
- WHO/IPCS's "HD_M^I" as a "harmonized" toxicity value
  - More refined definition of "RfD" applicable to both non-cancer and cancer endpoints
  - Quantitatively addresses magnitude of response, population variability, uncertainty
- Two Excel-based software tools for quickly and easily implementation
  - BMDS Wizard for dose-response modeling
  - APROBA for derivation of harmonized toxicity values
- Case studies with deoxynivalenol and methyleugenol
  - Feasibility of harmonized approach to dose-response assessment
  - Degree of human variability is the largest uncertainty

Resources

- U.S. EPA BMD technical guidance
  - http://www2.epa.gov/osa/benchmark-dose-technical-guidance
- U.S. EPA BMDS
  - http://www.epa.gov/ncea/bmds/
- ICF BMDS Wizard
  - http://www.icfi.com/insights/products-and-tools/bmds-wizard
- RIVM PROAST software
  - http://www.rivm.nl/en/Documents_and_publications/Scientific/Models/PROAST
- U.S. EPA Body weight ¾ scaling guidance
  - http://www2.epa.gov/osa/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose
- U.S. EPA Inhalation dosimetry methods
  - http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993
- WHO/IPCS Uncertainty guidance document and APROBA spreadsheet
  - http://www.who.int/ipcs/methods/harmonization/areas/hazard_assessment/en/
- Health Assessment Workspace Collaborative (HAWC)
  - https://hawcproject.org
- Selected publications
  - Wignall et al. 2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environ Health Perspect. 122(5):499-505. doi: 10.1289/ehp.1307539
  - Abdo et al. 2015. Population-based in vitro hazard and concentration-response assessment of chemicals: the 1000 genomes high-throughput screening study. Environ Health Perspect. 123(5):458-66. doi: 10.1289/ehp.1408775
  - Chiu WA, Slob W. 2015 A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects. Environ Health Perspect. doi: 10.1289/ehp.1409385

Appendix: Dose-response data used for case studies

Deoxynivalenol

Dose (mg/kg-d)	Mean Body Weight in g	Stdev	Number of Animals
0	43.85	2.69	37
0.1	43.51	2.86	35
0.5	40.04	3	43
1.1	35.09	2.56	42

Iverson F, Armstrong C, Nera E, Truelove J, Fernie S, Scott P et al. (1995). Chronic feeding study of deoxynivalenol in B6C3F1 male and female mice. Teratog Carcinog Mutagen. 15(6):283–306.

Excel files:
DON-APROBA.xlsx
DON-casestudy-BMDS Wizard.xlsm

Note: BMDS Wizard files require EPA BMDS installation

Methyleugenol

Dose (mg/kg-d)	Incidence of liver tumors	Number of Animals
0	7	50
26	14	50
54	28	50
110	43	50
210	45	50

NTP (2000). Toxicology and carcinogenesis studies of methyleugenol (CAS No. 93-15-2) in F344/N rats and B6C3F1 mice (gavage studies). TR-491. National Toxicology Program. U.S. Department of Health and Human Services. Research Triangle Park.

Excel files:
MET-APROBA.xlsx
MET-casestudy-BMDS Wizard.xlsm
MET-BMR01-APROBA.xls
MET-casestudy-BMD01-BMDS Wizard.xlsm