

Advancing Dose-Response Analyses and Tools

Board of Scientific Counselors (BOSC) Subcommittee Chemical Safety for Sustainability (CSS) and Health and Environmental Risk Assessment (HERA) National Research Programs Virtual Meeting on February 2-5, 2021

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February 5, 2021

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Office of Research and Development Center for Public Health and Environmental Assessment

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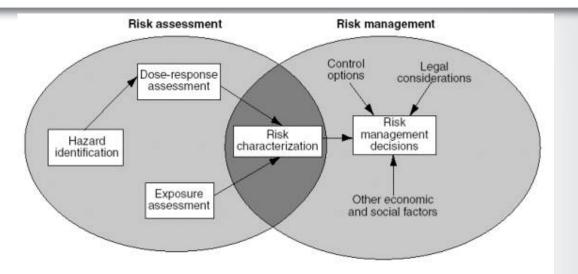
Advancing Dose-Response Analysis and Tools

Characterizing dose-response relationships is fundamental to health risk assessment

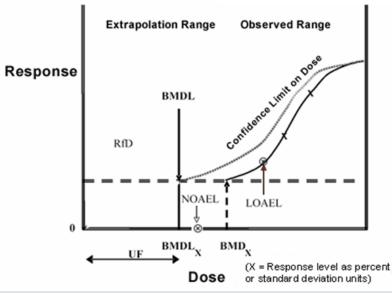
Models are used to extrapolate from the observed range, often well above environmental levels, to the range representing human exposures

Characterizing dose is of key importance, but very challenging for inhalation exposures

Characterizing uncertainty is essential for effective interpretation of model results



Source: EPA Office of Research and Development.





Coordinated Approach to Research, Tools, and Training

• Research – Focused in Output 3.5

- 3.5.1 Research in support of informative parameter priors used in Bayesian model averaging of dichotomous and continuous endpoint (Allen Davis's presentation)
- 3.5.2 Development of multivariate benchmark dose modeling for traditional toxicological and toxicogenomic data
- 3.5.3 Development of a unified model suite for dichotomous and continuous toxicological data
- 3.5.4 Advancement of nested dose-response modeling for developmental toxicity data
- 3.5.5 Characterizing Determinants of Risk: Concentration, Duration and Timing of Exposure
- 3.5.6 Case Studies and Advancements in Uncertainty Analysis (Todd Blessinger's presentation)
- And more in Appendix B, Part 2

• Tools – Focused in Output 4.1

- 4.1.3 Development, Operation, and Interoperability of Existing and Implementation of Planned Critical Components of BMDS and CatReg (Allen Davis's presentation)
- 4.1.5 All Ages Lead Model
- 4.1.6 Evaluation of the Integrated Exposure Uptake Biokinetic (IEUBK) Model version 2.0
- 4.1.7 Multi-path Particle Dosimetry (MPPD) model (Annie Jarabek's presentation)

• Training – Focused in Output 4.2

- 4.2.1 Risk Assessment Training to Improve the Harmonization and Collaboration between ORD and EPA Regional/Program Offices, State/Local/Tribal Agencies, and International Organizations (Annie Jarabek's presentation)
- 4.2.3 Development and Maintenance of BMDS and CatReg Documentation and Training Manual



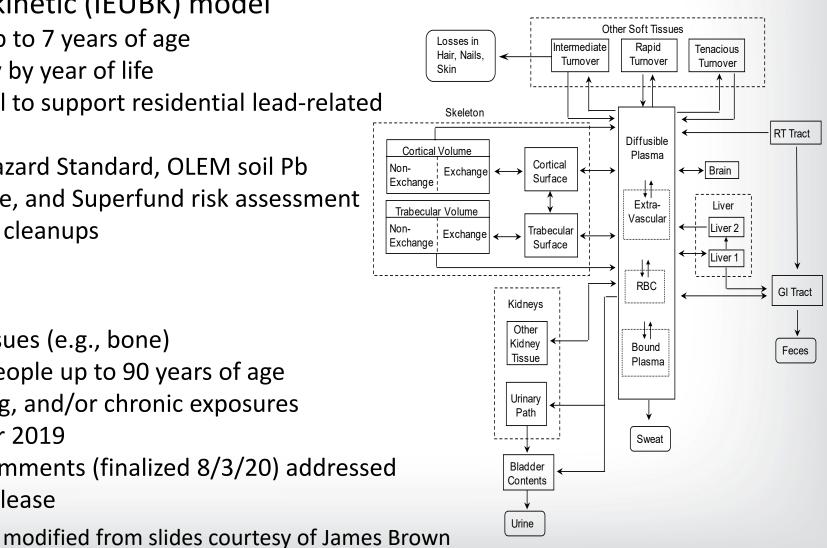
EPA Pb exposure and biokinetic models led by HERA scientists

Integrated Exposure Uptake Biokinetic (IEUBK) model

- Estimates Pb in blood of children up to 7 years of age
- Steady state exposure that can vary by year of life
- Recommended risk assessment tool to support residential lead-related site cleanups
- Used to support OPPT Lead Dust Hazard Standard, OLEM soil Pb guidance, OW Lead and Copper Rule, and Superfund risk assessment tool to support residential lead site cleanups

All Ages Lead Model (AALM)

- Estimates Pb in blood and other tissues (e.g., bone)
- Extends modeling capabilities for people up to 90 years of age
- Allows acute, transiently reoccurring, and/or chronic exposures
- Underwent EPA SAB review October 2019
- Public release planned after SAB comments (finalized 8/3/20) addressed
- Anticipated wide use after public release







Advancing D	ose-Response	Analyses a	nd Tools

12:20 – 12:35	Advancing Dose-Response Intro with Charge Question	John Vandenberg, CPHEA
12:35 – 12:55	Multi-path Particle Dosimetry Model	Annie Jarabek, CPHEA
12:55 – 1:15	Bayesian Model Averaging and BMDS 3.2	Allen Davis, CPHEA
1:15 – 1:35	Approximate Probabilistic Analysis (APROBA)	Todd Blessinger, CPHEA
1:35 – 2:10	BOSC Subcommittee discussion and Qs/As	Katrina Waters, Chair



Charge Question

Dose-response modeling is a critical step in human health assessment. Existing methods have improved upon older methodologies; however, unresolved issues, uncertainties, and complications remain that require targeted research. HERA has proposed research products that will result in dose-response methods that are more precise, robust, and meet varied needs. Is it clear how these planned products address important issues in dose-response modeling with an application to risk assessment? What suggestion(s) or recommendation(s) does the Subcommittee offer to continue to advance methods in doseresponse modeling with an application to risk assessment? [Research Area 3, Output 3.5 and Research Area 4, Output 4.1]



EPA Multi-path Particle Dosimetry (MPPD) Model 2021 (v. 1.01) Technical Support Documentation & User's Guide

Annie M. Jarabek

Human and Environmental Effects Assessment Division

CPHEA

Advancing Dose-Response Analyses and Tools

HERA Session 3

February 5, 2021

US EPA Board of Scientific Counselors Chemical Safety Subcommittee Meeting





- Modernizing our assessment toolbox: Advancing evidence integration
- Why: Choice of MPPD model
- What: New EPA-specific software with technical support & user's guide
- Who: Collaborators in development and application
- How: Role in risk assessment use case applications in OCSPP
- When: Next steps
- Roll out: Risk assessment training
- Summary

Disclaimer: These views are those of the author and do not represent US EPA policy.

Modernizing our Assessment Toolbox

>Advancing evidence integration: Dosimetry adjustments aid exposure alignment

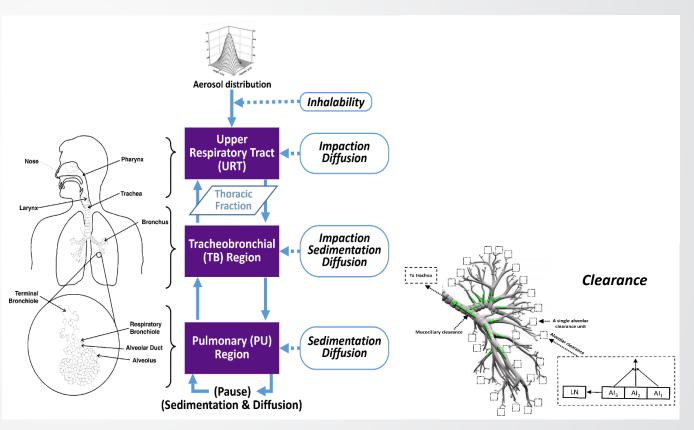
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Consist	tent Exposure M	etrics For Alignin	g Exposure-Res	ponse Across S	Systems

NAS (2017). Using 21st Century Science to Improve Risk-Related Evaluations <u>http://www.nap.edu/24635</u>

SEPA Why: Choice of MPPD Model

- Particle model in current use was developed in 1994 as part of the inhalation reference concentration (RfC) methodology
- Particle dosimetry modeling has matured
 - Additional algorithms: Inhalability
 - Move from empirical to mechanistic description of deposition
 - Clearance to predict retained dose
- Applied Research Associates, Inc. has developed many versions for various clients
 - EPA users confused regarding differences
 - External partners (states, NGO, academics) also need guidance
- Support consistent use across the Agency programs



What: EPA MPPD 2021 (v.1.01)

- New EPA version of the MPPD model software
 - Revised graphical user's interface (GUI)
 - Some updated algorithms

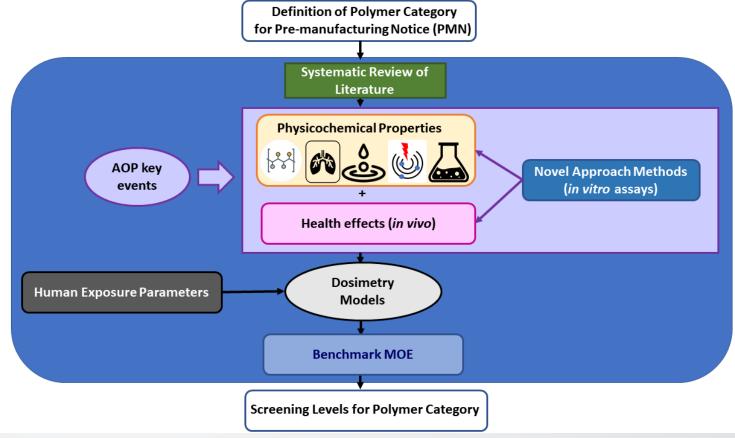
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- Technical support documentation and user's guide
 - Introduction to inhalation dosimetry
 - Step-by-step explanation of input fields
 - Guidance on input parameters and procedures
 - Specific use case illustrations
- Agency deployment requires external peer review



SepaWho: Development and Application

- Collaborative development
 - Annie M. Jarabek, US EPA ORD, CPHEA HEEAD
 - Bahman Asgharian, Applied Research Associates, Inc., Raleigh, NC
 - Fred Miller, Fred Miller, LLC
 - Owen Price, Applied Research Associates, Inc., Arlington, VA
- Application: Premanufacturing notice (PMN) program in OPPT
- Additional use case applications: TSCA



Integrated Approach to Testing and Assessment (IATA)

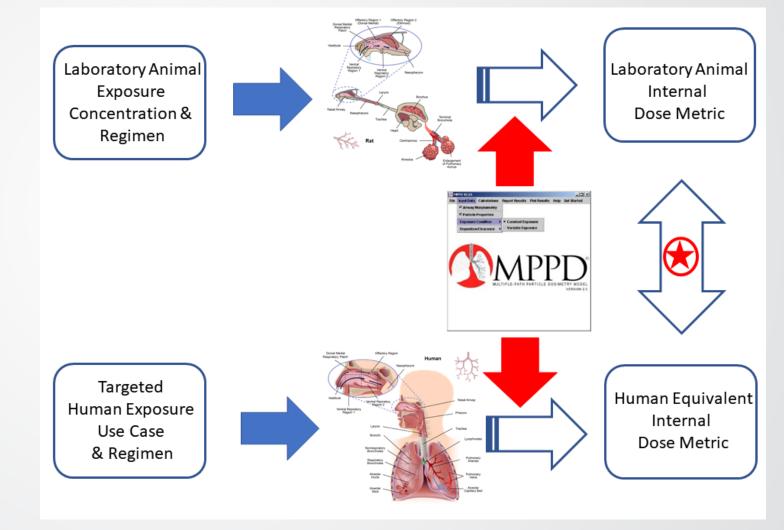
Jarabek, Stedeford et al. (accepted)

How: Role in Risk Assessment

Interspecies
 extrapolation: human
 equivalent
 concentration (HEC)

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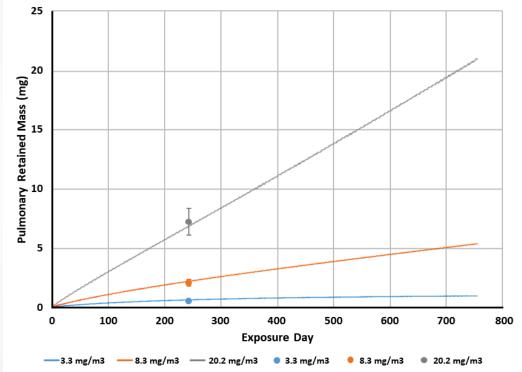
- Improved characterization of target human scenario
 - Specific size, distribution, density and exposure data
 - Replace default parameters and equations



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Use Case: Particle Overload

- Particle overload: When particles overwhelm ability of alveolar macrophages to clear from pulmonary region
- A kinetic phenomenon that creates context for consideration of observed toxicity, e.g., rat lung tumors not considered relevant due to differences in clearance rates
- Novel deployment of MPPD to demonstrate overload occurrence to define new pre-manufacturing notice (PMN) categories for read-across and inform risk evaluations (manuscripts accepted in ACS' Chem Res Toxicol and abstracts submitted for presentations at SOT 2021)
 - Poorly Soluble, Low Toxicity (PSLT) Polymer Category: An Integrated Approach to Testing and Assessment (IATA) Including New Approach Methods(NAMs) under the Toxic Substances Control Act (TSCA). A. M. Jarabek¹, T. Stedeford², G. S. Ladics³, O. T. Price⁴, A. Tveit⁵, M. P. Hayes⁶, R. T. Tremblay⁷, S. A. Snyder⁸, K. D. Salazar², S. Osman-Sypher⁹, W.Irwin², M. Odin¹⁰, J. Melia¹⁰, H. Carlson-Lynch¹⁰, M. Sharma¹¹, A. J. Clippinger¹¹, A. O. Stucki¹¹, and T. R. Henry². ¹US EPA, Research Triangle Park, NC; ²US EPA,Washington, DC; ³Dupont Nutrition and Biosciences, Wilmington, DE; ⁴Applied Research Associates Inc., Arlington, VA; ⁵BASF Corporation, Florham Park, NJ;⁶Procter & Gamble, Mason, OH; ⁷Procter & Gamble, Strombeek-Beaver, Belgium; ⁸Covestro LLC, Pittsburgh, PA; ⁹American Chemistry Council, Washington, DC;¹⁰SRC Inc., North Syracuse, NY; and ¹¹PETA International Science Consortium Ltd., London, United Kingdom.
 - Surfactants Category: An Integrated Approach to Testing and Assessment (IATA) Including New Approach Methods (NAMs) for Assessing InhalationRisks under the Toxic Substances Control Act (TSCA). T. R. Henry¹, K. D. Salazar¹, M. P. Hayes², W. Kennedy³, A. M. Keene³, A. M. Jarabek⁴, O. T. Price⁵, S. Moors⁶, L. Jovanovich⁷, J. L. Rose⁸, A. Tveit⁹, R. T. Tremblay¹⁰, R. A. Becker¹¹, S. Osman-Sypher¹¹, P. D. McMullen¹², S. D. Slattery¹², W. Irwin¹, M. Odin¹³, J. Melia¹³, M. Sharma¹⁴, A. J. Clippinger¹⁴, A. Stucki¹⁴, and T.Stedeford¹. ¹US EPA, Washington, DC; ²Procter & Gamble, St. Bernard, OH; ³Afton Chemical Corporation, Richmond, VA; ⁴US EPA, Research Triangle Park, NC; ⁵Applied Research Associates, Inc., Arlington, VA; ⁶BASF Corporation, Duesseldorf, Germany; ⁷Stepan Company, Northfield, IL; ⁸Procter & Gamble, Mason, OH; ⁹BASF Corporation, Florham Park, NJ; ¹⁰Procter & Gamble, Strombeek-Beaver, Belgium; ¹¹American Chemistry Council, Washington, DC; ¹²ScitoVation, Durham,NC; ¹³SRC Inc., North Syracuse, NY; and ¹⁴PETA International Science Consortium Ltd., London, United Kingdom.



Jarabek, Stedeford et al. (accepted)

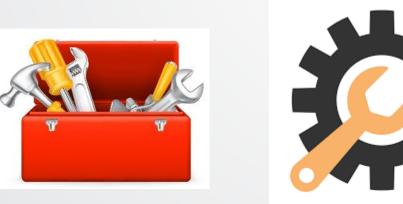
EPA Rollout: Risk Assessment Training

- Didactic and experiential modules with experts to convey scientific subject matter and methodologies
- Collaboration with OCSPP to update for TSCA applications
- MPPD training will be one module within a set covering inhalation issues:
 - Inhalation toxicology
 - Inhalation dosimetry modeling (both particles and different gases)
 - MPPD model for particle dosimetry



EPA When: Next Steps

- Release of external peer review document:
- Virtual public comment and peer review meeting:
- Revision based on peer panel recommendations:
- Development and deployment of training:
- On-going maintenance and support as part of HERA program
- Build workbench to integrate dosimetry into assessment workflows

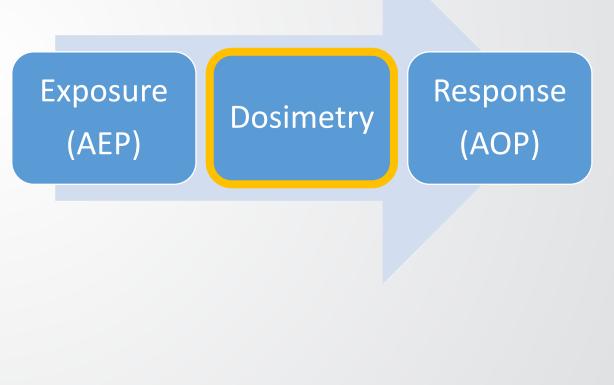




March 2021 April 2021 Fall 2021 Spring 2021 **SEPA**

Summary

- Dosimetry modeling is critical link to translate exposure to internal dose for response analysis
 - Exposure alignment for evidence integration
 - Application of NAMs
- MPPD model in toolbox will build capacity to bring dosimetry directly into assessment workflows
- Collaborative development by use cases and training ensures consistent and coherent application in assessments across programs



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Benchmark Dose Modeling – Bayesian Model Averaging

Allen Davis, MSPH

Center for Public Health and Environmental Assessment, U.S. EPA

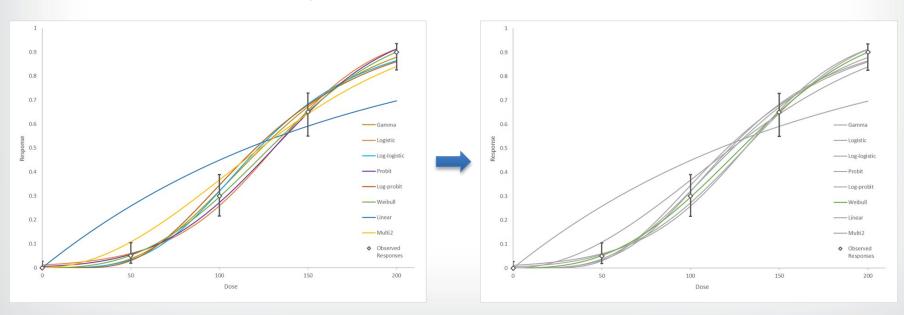


The views expressed in this presentation are those of the author(s) and do not necessarily reflect the views or policies of the US EPA.

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Single Model Selection

- When fitting multiple models to a single dataset, many models can (<u>and often will</u>) statistically fit the data well
 - So, is there a compelling reason (toxicology, MOA, etc.) to pick one model over any other?
 - Or (most commonly) is the model selected based on pure statistical fit?
 - This is model uncertainty



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Addressing Model Uncertainty

- Multiple approaches have been developed for addressing and/or characterizing model uncertainty
 - Flexible parametric models some research has indicated that some models (Exponential 5) are flexible enough to fit the majority of dose-response shapes observed in the literature
 - Semi- or non-parametric models completely data-driven models that are hyperflexible
 - Model averaging methods by which the results of a suite of individual models are averaged together to give one estimate of the BMD and BMDL; consistent with modeling approaches recommended by WHO and implemented by European partners (EFSA, RIVM)

BMDS Bayesian Model Averaging

Unique aspects of EPA/NIOSH model averaging approach:

Informed priors

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- Based on where the BMD_{10} estimates are most likely to be relative to a study's maximum dose
- Disentangle issues related to models that "degenerate" to other models (Weibull, etc.)
- Prevent over-fitting of individual models
- Provides a single standard set of priors in BMDS (i.e., Excel version) that gives reasonable, health-protective, consistent, and reproducible results
- Research on priors is part of current HERA research portfolio (HERA 3.5.1)
- Laplace approximation of posterior density
 - Minimal loss of accuracy or reliability
 - Substantial increase in speed (~10-fold faster than MCMC approaches implemented in other platforms)
 - Increases in speed are critically important for batch analyses of many datasets

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Focused Prior

 Instead of looking at priors over all model parameters, or specific parameters, place a reasonable prior over the value of ultimate interest, the BMD

• Benefits:

- All models are wrong, so the parameters are abstract entities. We are ultimately
 interested in the value of the BMD
- In terms of maximum tolerated dose and dose-response study design, the value of the BMD can be expressed as a percentage of the maximum tolerated dose.

Issues:

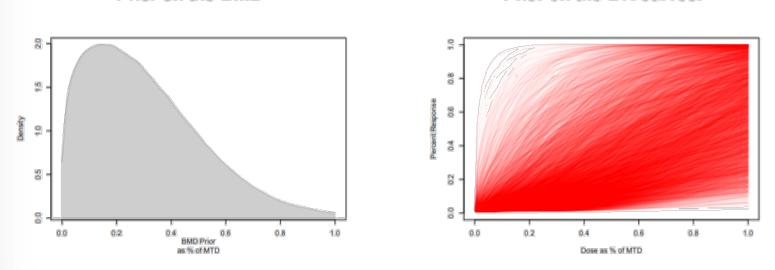
- Can be perceived as subjective in terms of what is "right"
- Significant prior impact in low data cases
- Might change based upon target quantity (i.e., may be different for BMR = 10% vs. BMR = 1%)



Prior on the BMD

Here, assuming a prior on the BMD such that the majority is between
 0 and 0.5 of the MTD

Prior on the DR curves.



 In BMDS 3.2 (and later versions) priors for dichotomous models are set such that the BMD is expected to fall within ~0.2-0.5 of the MTD

BMDS Bayesian Model Averaging

- Maximum a-posteriori find the maximum of the posterior distribution and use a normal like approximation
 - Very fast computationally compared to Markov Chain Monte Carlo (MCMC)
 - Accurate for the right-sized posterior

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- BMDS uses the Laplace approximation to the marginal density of the data as model weights
- The model-averaged BMD point estimate is the weighted average of the MAP estimates from individual models
- BMDL and BMDU values are estimated similar to the profile likelihood approach except that the posterior density is profiled
- Method is fully described in Risk Analysis paper: Quantitative risk assessment: developing a Bayesian approach to dichotomous dose-response uncertainty. Risk Analysis 40(9). DOI: 10.1111/risa.13537

SEPA BMDS Bayesian Model Averaging

- EPA/NIOSH BMA approach was extensively tested against I) MCMC Bayesian MA approach with uninformative priors; 2) BMDS using 2012 model selection criteria; and 3) flexible non-parametric model
- 34 separate "true-dose" curves used to test approaches

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True BMD	BMA	BMDS	NP	мсмс
All templates	70.6%	41.2%	76.5%	47.1%
True BMD < 0.2x max dose	63.2%	26.3%	57.9%	36.8%
True BMD > 0.2x max dose	80%	60%	100%	60%
True BMD < 0.1x max dose	60%	30%	20%	40%
True BMD > 0.1x max dose	75%	45.8%	100%	50%

Percentage of Times BMDL Coverage is >90% than True BMD Value



BMDS User Interface

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Using BMDS – Add Option Sets

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Using BMDS – Modeling Summary Results

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	Dose	N	Incidence			Examples of	of how to u	se BMDS 3.2	for		Recommended	frequentist model		
	Dose	N	Incidence			dichotomo	ous, continu	ous, dichotor	nous cancer,		Model	averaging		
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	Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	P Value	AIC	Unnormalized Log Posterior	Scaled Residual for Dose Group near	Scaled Residual for	
		7 maryolo Type									Probability	BMD	Control Dose Group	BMDS
	Dichotomous Hill	frequentist	Restricted	Extra Risk	0.1	15.85789	7.897094	29.144824	0.6945918		Probability -	BMD -0.067756196	Control Dose Group -0.00062655	
	Dichotomous Hill Gamma				0.1	15.85789 19.33104	7.897094 14.31304		0.6945918 0.9892812		Probability - -	BMD		Via
		frequentist	Restricted	Extra Risk Extra Risk Extra Risk	0.1 0.1	19.33104 15.85789	14.31304 9.584413	29.144824 30.451431 29.14482	0.9892812 0.9258161	94.36832933 98.23575637	-	BMD -0.067756196	-0.00062655	Via Via Via
	Gamma Log-Logistic Multistage Degree 4	frequentist frequentist	Restricted Restricted	Extra Risk Extra Risk	0.1	19.33104	14.31304 9.584413 14.31258	29.144824 30.451431 29.14482	0.9892812 0.9258161 0.9892812	94.36832933 98.23575637 94.36832933	-	BMD -0.067756196 0.274786155	-0.00062655 -0.000617049	Via Via Via
	Gamma Log-Logistic Multistage Degree 4 Multistage Degree 3	frequentist frequentist frequentist	Restricted Restricted Restricted	Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk	0.1 0.1 0.1 0.1	19.33104 15.85789 19.33104 19.33104	14.31304 9.584413 14.31258 14.31291	29.144824 30.451431 29.14482 36.20013 36.19987	0.9892812 0.9258161 0.9892812 0.9892812	94.36832933 98.23575637 94.36832933 94.36832933	-	BMD -0.067756196 0.274786155 -0.06775637 0.274786146 0.274786164	-0.00062655 -0.000617049 -0.000623993 -0.000617049 -0.000617049	Via Via Via Via Via
	Gamma Log-Logistic Multistage Degree 4 Multistage Degree 3 Multistage Degree 2	frequentist frequentist frequentist frequentist	Restricted Restricted Restricted Restricted Restricted Restricted	Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk	0.1 0.1 0.1 0.1 0.1	19.33104 15.85789 19.33104 19.33104 19.33104	14.31304 9.584413 14.31258 14.31291 14.31285	29.144824 30.451431 29.14482 36.20013 36.19987 36.20013	0.9892812 0.9258161 0.9892812 0.9892812 0.9892812	94.36832933 98.23575637 94.36832933 94.36832933 94.36832933		BMD -0.067756196 0.274786155 -0.06775637 0.274786146 0.274786164 0.274786165	-0.00062655 -0.000617049 -0.000623993 -0.000617049 -0.000617049 -0.000617049	Via Via Via Via Via Via
	Gamma Log-Logistic Multistage Degree 4 Multistage Degree 3 Multistage Degree 2 Multistage Degree 1	frequentist frequentist frequentist frequentist frequentist	Restricted Restricted Restricted Restricted Restricted	Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk	0.1 0.1 0.1 0.1 0.1 0.1	19.33104 15.85789 19.33104 19.33104 19.33104 19.33104	14.31304 9.584413 14.31258 14.31291 14.31285 14.3126	29.144824 30.451431 29.14482 36.20013 36.19987 36.20013 27.640746	0.9892812 0.9258161 0.9892812 0.9892812 0.9892812 0.9584861	94.36832933 98.23575637 94.36832933 94.36832933 94.36832933 96.36832933		BMD -0.067756196 0.274786155 -0.06775637 0.274786146 0.274786164 0.274786165 0.274786131	-0.00062655 -0.000617049 -0.000623993 -0.000617049 -0.000617049 -0.000617049 -0.000617049	Vie Vie Vie Vie Vie Vie Vie
	Gamma Log-Logistic Multistage Degree 4 Multistage Degree 3 Multistage Degree 2 Multistage Degree 1 Weibull	frequentist frequentist frequentist frequentist frequentist frequentist	Restricted Restricted Restricted Restricted Restricted Restricted Restricted	Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk	0.1 0.1 0.1 0.1 0.1 0.1 0.1	19.33104 15.85789 19.33104 19.33104 19.33104 19.33104 19.33104	14.31304 9.584413 14.31258 14.31291 14.31285 14.3126 14.31304	29.144824 30.451431 29.14482 36.20013 36.19987 36.20013 27.640746 30.842788	0.9892812 0.9258161 0.9892812 0.9892812 0.9892812 0.9584861 0.9584861	94.36832933 98.23575637 94.36832933 94.36832933 94.36832933 96.36832933 96.36832933	- - - - - -	BMD -0.067756196 0.274786155 -0.06775637 0.274786146 0.274786164 0.274786165 0.274786131 0.274786138	-0.00062655 -0.000617049 -0.000623993 -0.000617049 -0.000617049 -0.000617049 -0.000617049 -0.000619786 -0.000617187	Vie Vie Vie Vie Vie Vie Vie Vie Vie
	Gamma Log-Logistic Multistage Degree 4 Multistage Degree 3 Multistage Degree 2 Multistage Degree 1	frequentist frequentist frequentist frequentist frequentist frequentist frequentist	Restricted Restricted Restricted Restricted Restricted Restricted Restricted	Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk	0.1 0.1 0.1 0.1 0.1 0.1	19.33104 15.85789 19.33104 19.33104 19.33104 19.33104	14.31304 9.584413 14.31258 14.31291 14.31285 14.3126	29.144824 30.451431 29.14482 36.20013 36.19987 36.20013 27.640746	0.9892812 0.9258161 0.9892812 0.9892812 0.9892812 0.9584861	94.36832933 98.23575637 94.36832933 94.36832933 94.36832933 96.36832933 96.36832933	- - - - - - -	BMD -0.067756196 0.274786155 -0.06775637 0.274786146 0.274786164 0.274786165 0.274786131	-0.00062655 -0.000617049 -0.000623993 -0.000617049 -0.000617049 -0.000617049 -0.000617049	Vie Vie Vie Vie Vie Vie Vie Vie Vie
	Gamma Log-Logistic Multistage Degree 4 Multistage Degree 3 Multistage Degree 2 Multistage Degree 1 Weibull	frequentist frequentist frequentist frequentist frequentist frequentist frequentist frequentist	Restricted Restricted Restricted Restricted Restricted Restricted Restricted	Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk Extra Risk	0.1 0.1 0.1 0.1 0.1 0.1 0.1	19.33104 15.85789 19.33104 19.33104 19.33104 19.33104 19.33104 19.33104 55.96478	14.31304 9.584413 14.31258 14.31291 14.31285 14.3126 14.31304 43.343	29.144824 30.451431 29.14482 36.20013 36.19987 36.20013 27.640746 30.842788 71.751775	0.9892812 0.9258161 0.9892812 0.9892812 0.9892812 0.9584861 0.9584861 0.1446606	94.36832933 98.23575637 94.36832933 94.36832933 94.36832933 96.36832933 96.36832933	-	BMD -0.067756196 0.274786155 -0.06775637 0.274786146 0.274786164 0.274786165 0.274786131 0.274786138	-0.00062655 -0.000617049 -0.000623993 -0.000617049 -0.000617049 -0.000617049 -0.000617049 -0.000619786 -0.000617187	BMDS Via Via Via Via Via Via Via Via Via
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Using BMDS – Option Set Results

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16		Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	P Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Re
17		Dichotomous Hill	frequentist	Restricted	Extra Risk	0.1	15.85789	7.897094	29.144824	0.6945918	100.2357564	-	-0.067756196	-0.00062655	Viable
18		<u>Gamma</u>	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31304	30.451431	0.9892812	94.36832933	-	0.274786155	-0.000617049	Viable
19		Log-Logistic	frequentist	Restricted	Extra Risk	0.1	15.85789	9.584413	29.14482	0.9258161	98.23575637	-	-0.06775637	-0.000623993	Viable
20		Multistage Degree 4	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31258	36.20013	0.9892812	94.36832933	-	0.274786146	-0.000617049	Viable
21		Multistage Degree 3	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31291	36.19987	0.9892812	94.36832933	-	0.274786164	-0.000617049	Viable
22		Multistage Degree 2	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31285	36.20013	0.9892812	94.36832933	-	0.274786165	-0.000617049	Viable
23		Multistage Degree 1	frequentist	Restricted	Extra Risk	0.1	19.33104	14.3126	27.640746	0.9584861	96.36832933	-	0.274786131	-0.000619786	Viable
24		Weibull	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31304		0.9584861	96.36832933	-	0.274786138	-0.000617187	Viable
25		<u>Logistic</u>	frequentist	Unrestricted	Extra Risk	0.1	55.96478	43.343	71.751775	0.1446606	103.0027252	-	1.599996726	-1.362557141	Viable
26		Log-Probit	frequentist	Unrestricted	Extra Risk	0.1	-		25.715773	0.8052972		-	-0.227261455	-0.000617142	Viable - F
27		Probit	frequentist	Unrestricted	Extra Risk	0.1	51.68302		65.781622	0.1906352	102.1597545	-	1.485406079	-1.271842634	Viable
28		<u>Quantal Linear</u>	frequentist	Unrestricted	Extra Risk	0.1	19.33104		27.651236	0.9892812	94.36832933	-	0.274786154	-0.000617049	Viable
29		Dichotomous Hill	bayesian	-	Extra Risk	0.1	23.88815	10.16551	49.501684	-	-	-53.13822466	0.221120126	-0.855817711	
30		Gamma	bayesian	-	Extra Risk	0.1	26.35795		48.908685	-	-	-53.19703399	0.224861091	-0.943529669	
31		Logistic	bayesian	-	Extra Risk	0.1	55.08391		70.818903	-	-	-54.63520879	1.438333356	-1.511623327	
32		Log-Logistic	bayesian	-	Extra Risk	0.1	25.56395		52.479612	-	-	-52.62188353	0.226231253	-0.938424257	
33		Log-Probit	bayesian	-	Extra Risk	0.1	31.95571		64.871016	-	-	-54.19902941	0.617271666	-1.062742709	
34		Multistage Degree 4	bayesian	-	Extra Risk	0.1	29.70898	19.85807	46.212977	-	-	-56.57595301	0.336005674	-0.952118967	
35 36		Multistage Degree 3	bayesian bayesian	-	Extra Risk Extra Risk	0.1	28.01126 25.65265	18.92686	43.324266 39.31189	-	-	-53.23693243 -52.2005658	0.282571943 0.194760923	-0.936621658 -0.914261291	
36		Multistage Degree 2 Multistage Degree 1	bayesian bayesian	-	Extra Risk Extra Risk	0.1	25.65265		39.31189	-	-	-52.2005658	0.194760923	-0.914261291	
38		Probit	bayesian	-	Extra Risk	0.1	51.63621		65.922653	-	-	-53.92133341	1.435643794	-1.355140023	
39		Quantal Linear	bayesian	_	Extra Risk	0.1	21.51394		31.550179	-	-	-50.98970952	0.000679148	-0.870151483	
40		Weibull	bayesian	-	Extra Risk	0.1			58.812027	-	-	-53.25948327	0.343704366	-0.984798192	
41		Model Average	bayesian MA	-	Extra Risk	0.1			49.453226	_	-	-	-	-	
42		ModerAverage	sayesian MA		EAUGINISK	0.1	24.00520	11.74337	13.433220						
43															
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Using BMDS – Individual Model Results

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Model	frequentist Log-Probit v1.1		BMD	14.77267729				
Dataset Name	BMDS - training - Dichotomous		BMDL	6.267247615				
User notes	[Add user notes here]		BMDU	25.71577276	-			
			AIC	98.50125481	-			
Dose-Response Model	P[dose] = g+(1-g) * CumNorm(a+b*Log(Dose))		P-value D.O.F.	0.805297172 2	-			
Model Options			Chi ²	0.433087824	-			
Risk Type	Extra Risk		C	01100007021	1			
BMR	0.1		Model Para	ameters	1			
Confidence Level	0.95		# of Parameters	3	,			
Background	Estimated		Variable	Estimate				
			g	1.52346E-08				
Model Data			а	-2.890901327				
Dependent Variable	Dose		b	0.597653782				
Independent Variable	Incidence				7			
Total # of Observations	5		Goodness					
			Dose	Estimated	Expected	Observed	Size	Scaled
				Probability				Residual
			0	1.52346E-08	3.80864E-07	0	25	-0.000617
			20	0.026864535 0.135559224	0.671613383 3.388980604	1 3	25 25	0.4061993
			20 1	0.130009224	3.388980004	3	20	-0.22/201

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Using BMDS – Bayesian Model Averaging Results

Model Bayesian Model Averaging v1.0 Benchmark Dose Dataset Name BMDS - training - Dichotomous BMD 24.88927534 User notes [Add user notes here] BMDL 14.74397033 Model Options Risk Type Extra Risk BMDL 14.74397033 BMR 0.1 Confidence Level 0.95 23.88815284 10.1655111 49.50168 Confidence Level 0.95 Confidence Level 0.01343551 55.08390665 42.7697092 70.8189 Log-Logistic 0.104060774 25.56394637 10.7529737 52.47961 Log-Probit 0.027433821 51.0632071 17.665846 39.31189 Dependent Variable Dose Nutlistage 0.5134605448 21.51394337 15.5143648 31.55018	3 C	D	E F	G	Н	I	J	К	L	М
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Model Bayesian Model Averaging v1.0 Dataset Name BMDD - training - Dichotomous User notes [Add user notes here] Model Options [Add user notes here] Risk Type Extra Risk BMR 0.1 Confidence Level 0.95 Bacground Estimated Log-Logistic 0.0100607467 25.65394037 10.752973 Log-Probit 0.020781862 31.95570707 14.3543258 48.7102 Dependent Variable Dose Probit 0.020781862 31.95570707 14.3543258 49.31189 Dependent Variable Incidence 0.514605448 21.51394337 15.5143648 31.55018	Info			ſ	Benchmai	rk Dose]			
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Independent Variable Incidence Quantal Linear 0.514605448 21.51394337 15.5143648 31.55018	Model Data				Multistage	0.153322601	25.65264702	17.6865846	39.31189	
	Dependent Variable	Dose			Probit	0.027433821	51.6362071	40.6008542	65.92265	
	Independent Variable	Incidence			Quantal Linear	0.514605448	21.51394337	15.5143648	31.55018	
Total # of Observations 5 Weibull 0.053177041 29.45342064 12.7931193 58.81203	Total # of Observations	5			Weibull	0.053177041	29.45342064	12.7931193	58.81203	

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Next Steps

- Research into model averaging methods currently included in HERA research portfolio:
 - HERA 3.5.1 Research in support of informative parameter priors and used in Bayesian model averaging of dichotomous and continuous endpoints
 - HERA 3.5.3 Development of an updated model suite for dichotomous and continuous toxicological data
 - Outputs of these HERA products directly informs improvement of dichotomous model averaging and development of continuous model averaging

Development of Bayesian continuous model averaging is undergoing

- Allows for averaging across distributions if individual animal data is available
- Allows for averaging across variance models when assuming Normal distribution
- Planned for release with BMDS 3.4

Sepa

Quantitative Uncertainty Analysis & APROBA

Todd Blessinger, PhD

Center for Public Health and Environmental Assessment U.S. Environmental Protection Agency

> Presentation at BOSC 2021 February 5, 2021





Motivation

- Quantitative uncertainty analysis, such as moving towards "risk-specific dose" estimates, in human health assessments recommended by National Research Council (2009, 2014), especially for reference value derivation
 - Increases transparency
 - > Allows greater flexibility
- WHO/IPCS developed a method to estimate the uncertainty in a "target human dose" (2017 guidance document)



Current Reference Value Derivation

Reference values:

 $\succ \text{ RfV} = \frac{\text{POD}}{\text{UF}_1 \times \cdots \times \text{UF}_k}$

- POD: point of departure; UF: uncertainty factor
- Currently derived as point value ("deterministically")
- > WHO/IPCS approach is probabilistic.



Alternative Reference Value Derivation based on HD_{M}^{I}

- HD_M^I = the human dose at which a fraction (or incidence) I of the population experiences an effect of magnitude (or severity) M or greater for the critical effect considered.
- \geq <u>Ex</u>: Endpoint of interest: relative liver weight decrease
 - HD₀₅⁰¹ = dose at which 1% of the population experiences a decrease in relative liver weight of 5% or greater.



Alternative Reference Value Derivation based on HD_M^I

$$\succ HD_M^I = \frac{POD}{AF_1 \times \cdots \times AF_k}$$

- > POD: point of departure
- > AF_i's: "assessment factors"
- Point of departure and assessment factors are treated as random variables with probability distributions.
- > HD_M^I is a random variable.



Alternative Reference Value Derivation based on HD_M^I

- Allows estimation of "risk-specific dose"
 - > $\underline{\text{Ex:}}$ HD_{05}^{05} = dose at which 5% of the population experiences a decrease in relative liver weight of 5% or greater.



Approximate Probabilistic Analysis

- > Approximate Probabilistic Analysis (APROBA)
 - Excel-based tool for applying HD_M^I method
 - The point of departure and assessment factors are assumed to be independent and lognormally distributed.
 - > HD_{M}^{I} is lognormally distributed.



Approximate Probabilistic Analysis

- Provisional lognormal parameter values provided for commonly used assessment factors
 - Interspecies, duration extrapolation, interhuman variability
 - Based on empirical data
- Other parameter values can be entered



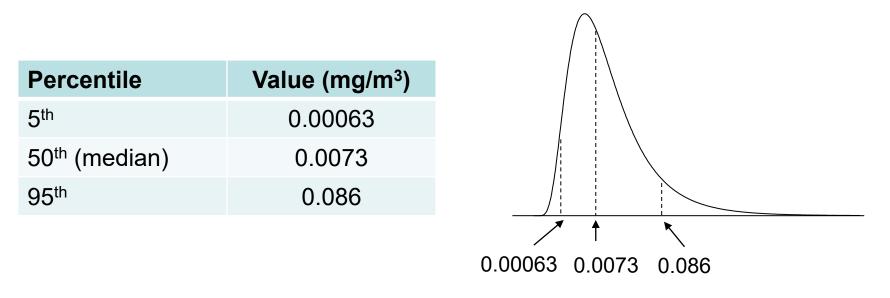
Application of APROBA to acrolein

- Application of APROBA to acrolein (Blessinger et al., 2020)
 - Endpoint: Incidence of lesions in the nasal respiratory epithelium, from Dorman et al. (2008)
 - Subchronic inhalation study in rats
 - Used I = 1% for incidence of nasal lesions of minimal severity
- HD_{minimal}⁰¹ = concentration that results in lesions of at least minimal severity in the nasal respiratory epithelium in 1% of a general human population.



Application of APROBA to acrolein

HD_{minimal}⁰¹ has lognormal distribution with estimated percentiles:



5th percentile = 0.00063 mg/m³ can be considered a "probabilistic reference concentration".



Risk-Specific Concentration

Risk-specific concentration: human incidence I can be adjusted

> Ex: For I = 5%, $HD_{minimal}^{05}$ percentiles

Percentile	Value (mg/m ³)
5 th	0.0015
50 th (median)	0.014
95 th	0.133



Next Steps

- \geq Expansion of APROBA and HD_M^I method:
 - Update provisional parameter values by collecting and analyzing additional toxicology data (current distributions too narrow?).
 - Relax the restriction of independent, lognormally distributed components (use numerical methods to estimate HD_M^I distribution).
 - Incorporate database uncertainty.



Summary & Conclusions

- HDMI method allows explicit, quantitative estimation of risk-specific dose.
- Quantitative uncertainty analysis methods require continual advancement.
- \geq Input from users is crucial.





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- WHO/IPCS (2017): Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd ed.
- Chiu WA & Slob W (2015): A unified probabilistic framework for dose-response assessment of human health effects. Environ Health Perspect 123(12):1241–1254.
- Blessinger et al. (2020): Application of a unified probabilistic framework to the dose-response assessment of acrolein Environ Int 143. Available online