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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Director, Health and Environmental Effects Assessment Division (HEEAD)

February 5, 2021

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

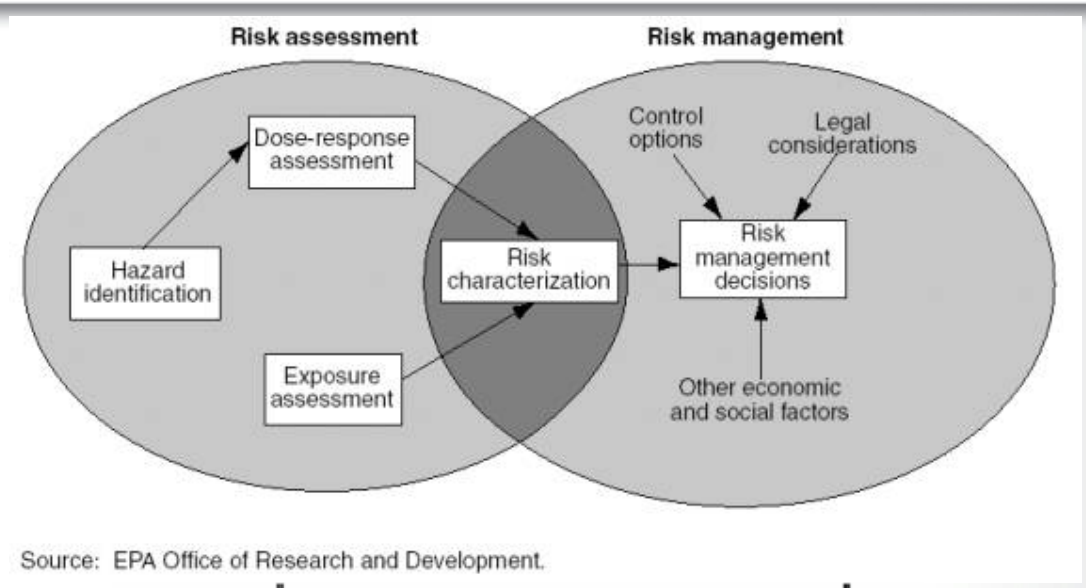
Advancing Dose-Response Analysis and Tools

Characterizing dose-response relationships is fundamental to health risk assessment

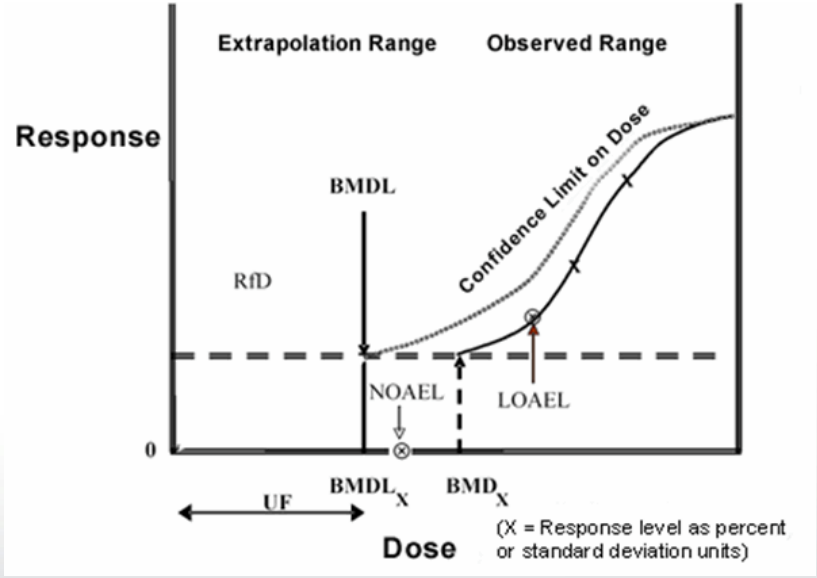
Models are used to extrapolate from the observed range, often well above environmental levels, to the range representing human exposures

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.



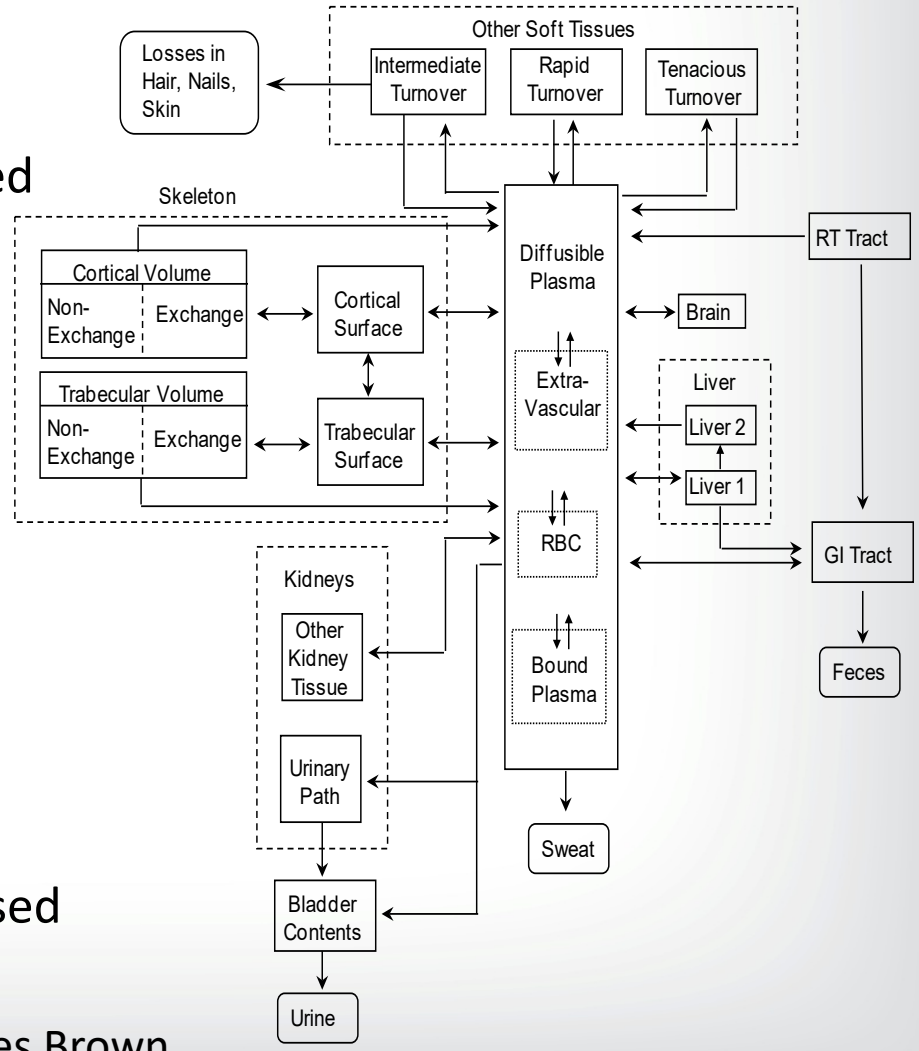
Coordinated Approach to Research, Tools, and Training

- **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

modified from slides courtesy of James Brown

HERA BOSC
Session 3

Advancing Dose-Response Analyses and 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 dose-response 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

US EPA Board of Scientific Counselors Chemical Safety Subcommittee Meeting

February 5, 2021

EPA at 50 Progress for a Stronger Future

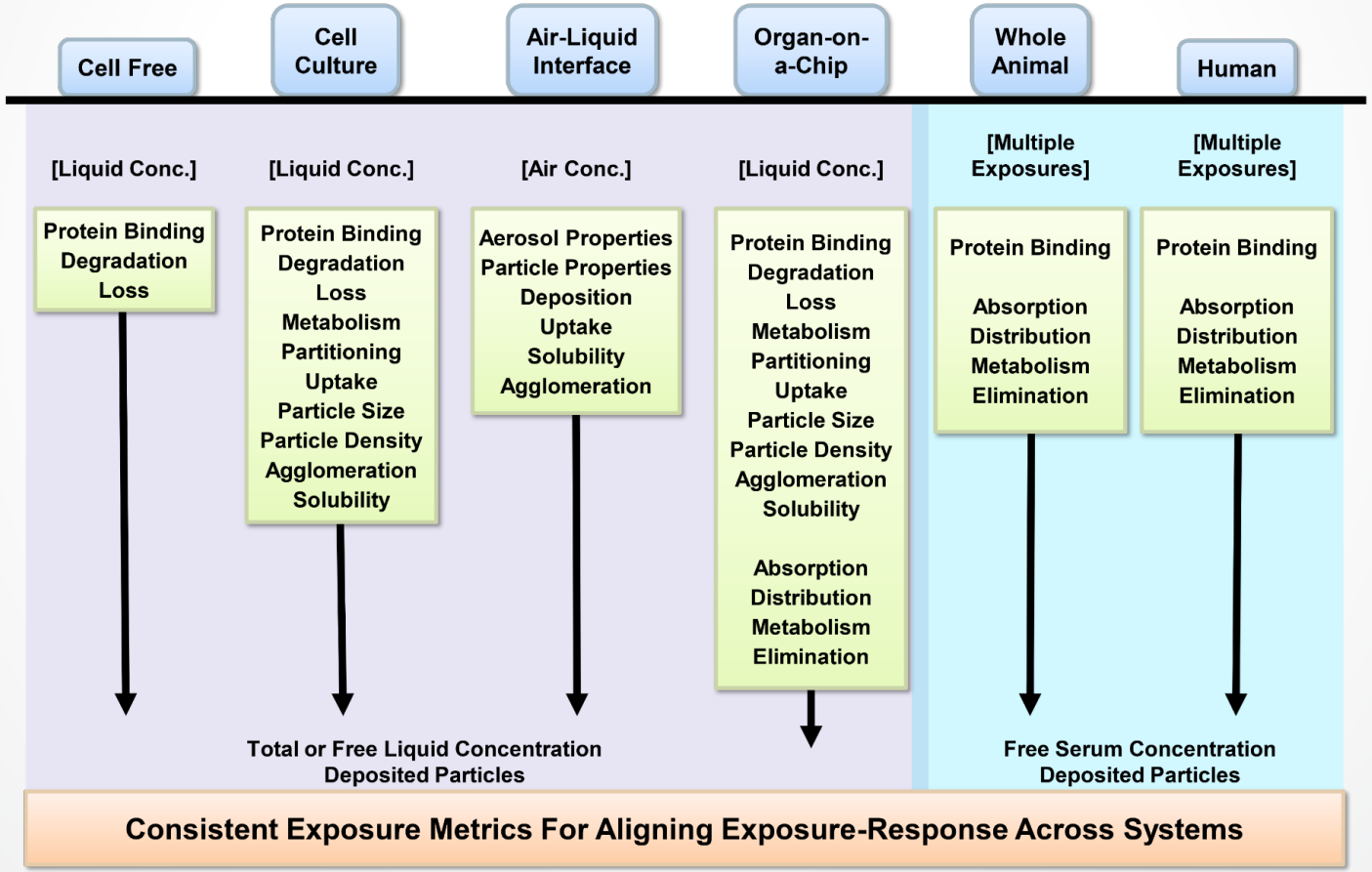
Overview

- 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

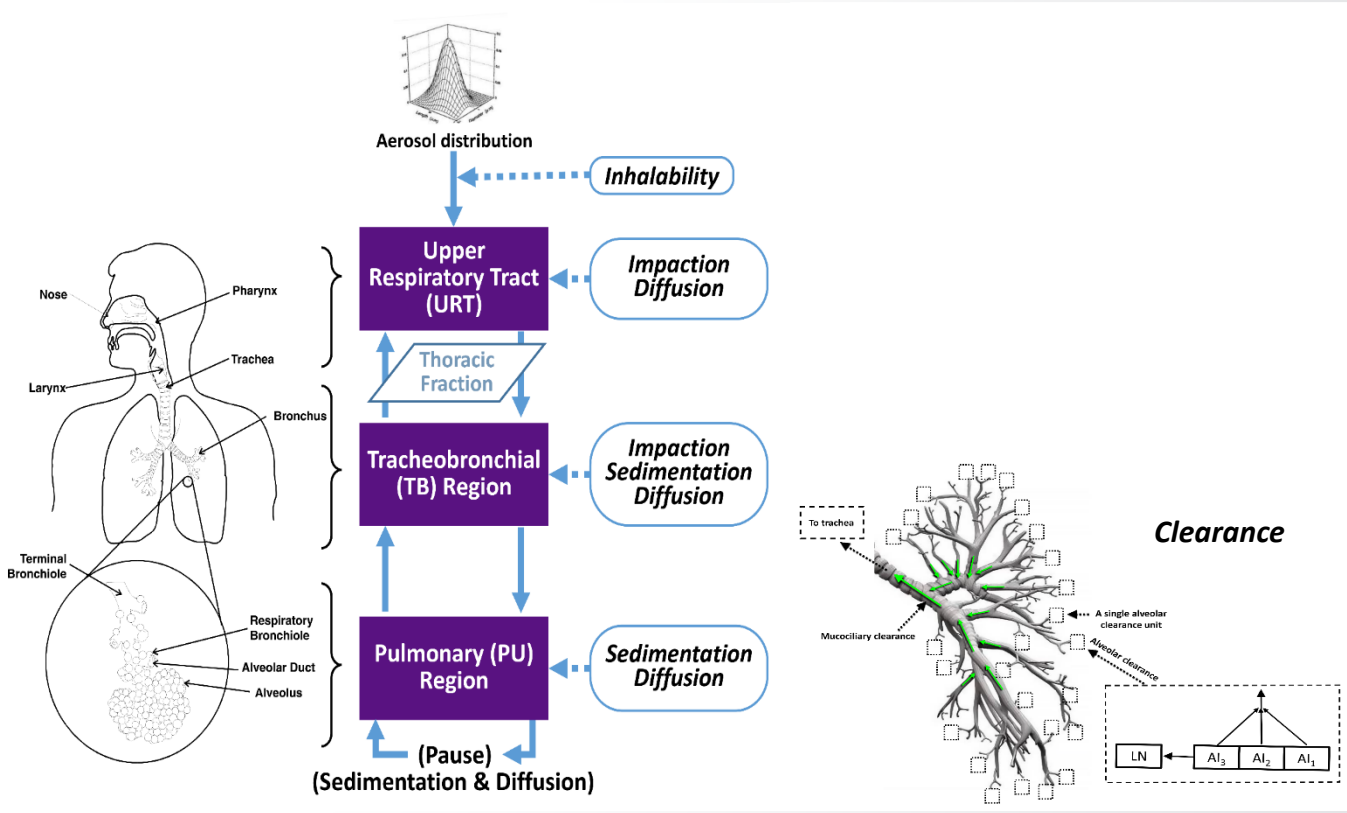
➢ *Advancing evidence integration: Dosimetry adjustments aid exposure alignment*



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

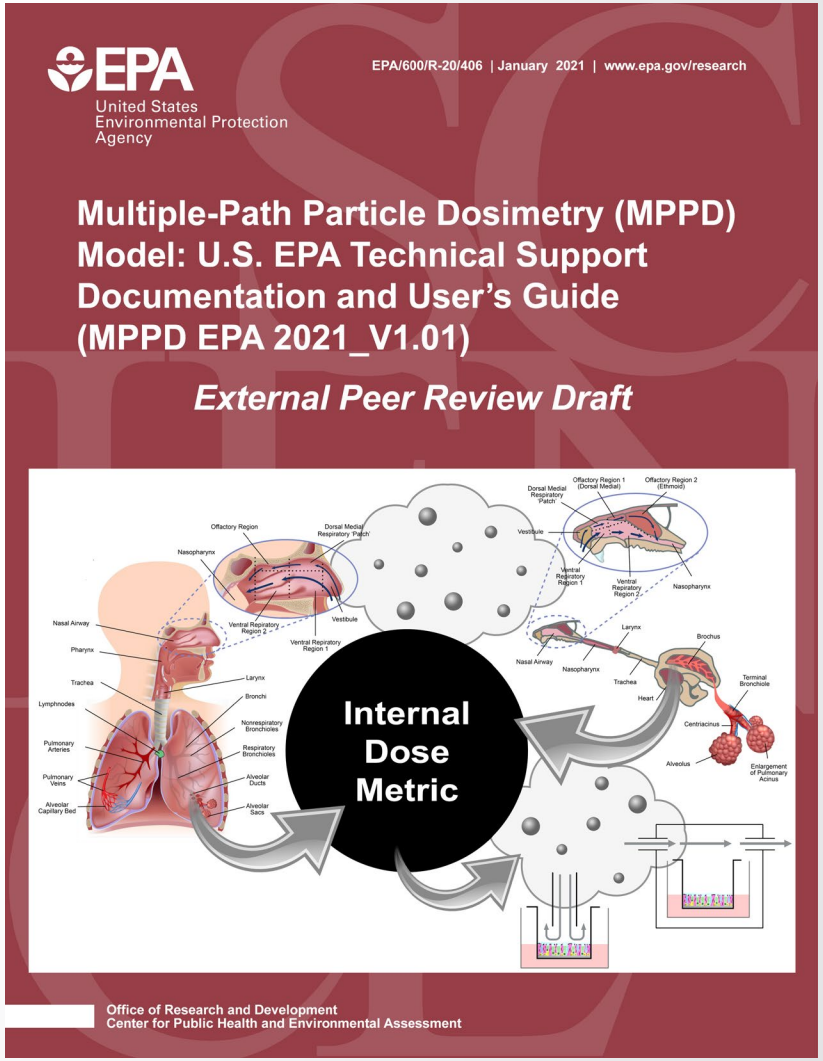
Why: Choice of MPPD Model

- 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)

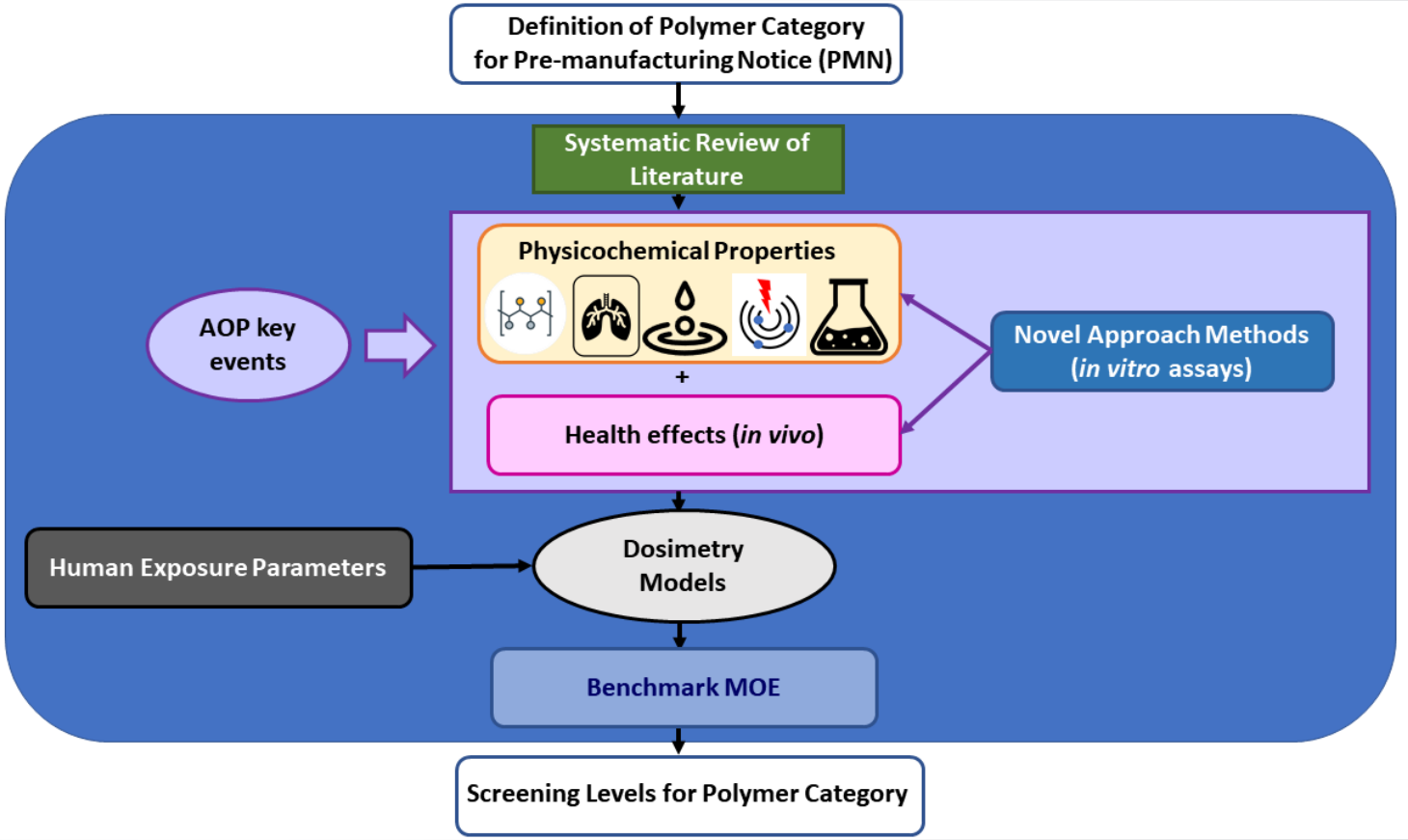
- New EPA version of the MPPD model software
  - Revised graphical user's interface (GUI)
  - Some updated algorithms
- Technical support documentation and user's guide
  - Introduction to inhalation dosimetry
  - Step-by-step explanation of input fields
  - Guidance on input parameters and procedures
  - Specific use case illustrations
- Agency deployment requires external peer review



Who: 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: Pre-manufacturing notice (PMN) program in OPPT
- Additional use case applications: TSCA

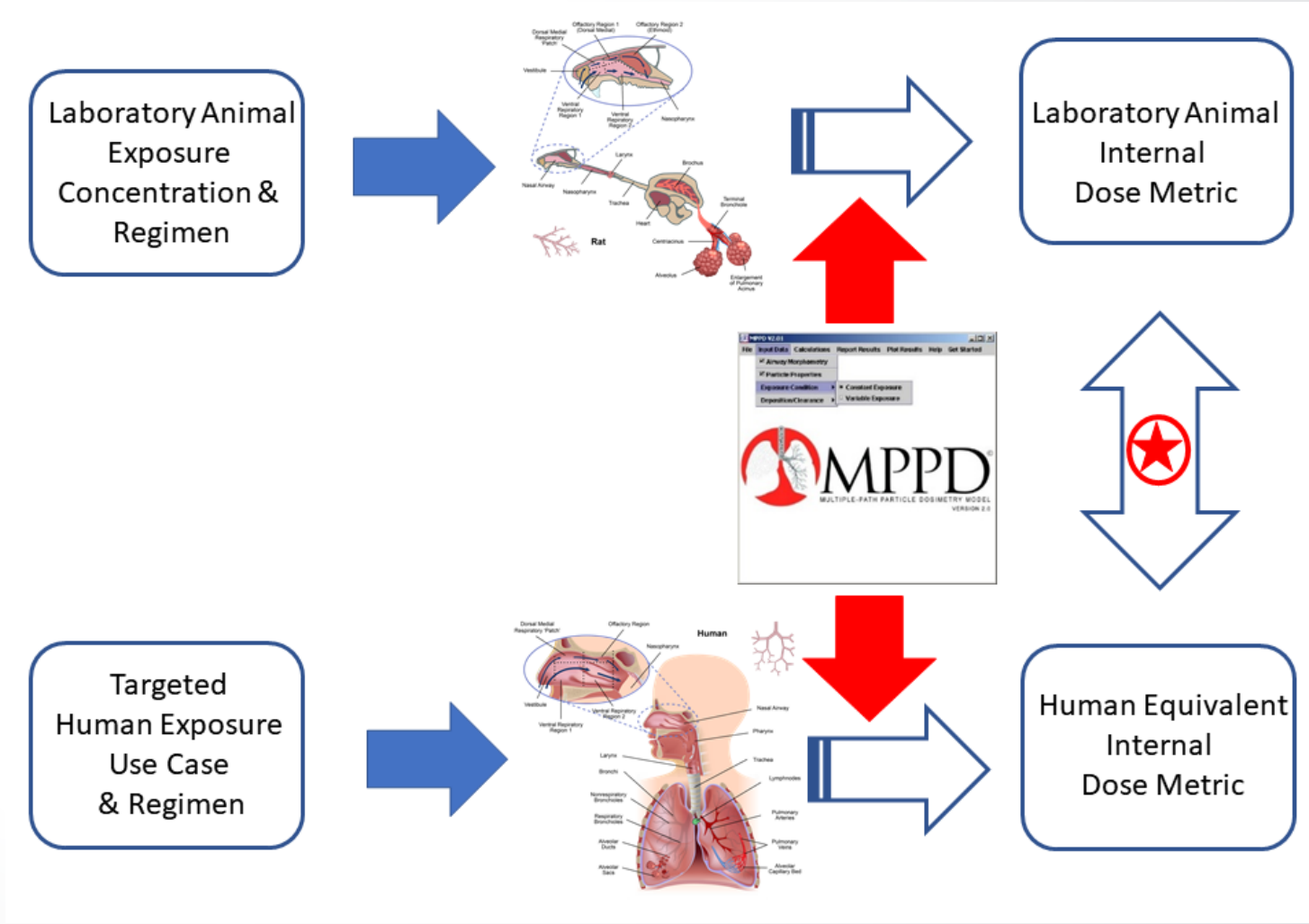
Integrated Approach to Testing and Assessment (IATA)



Jarabek, Stedeford et al. (*accepted*)

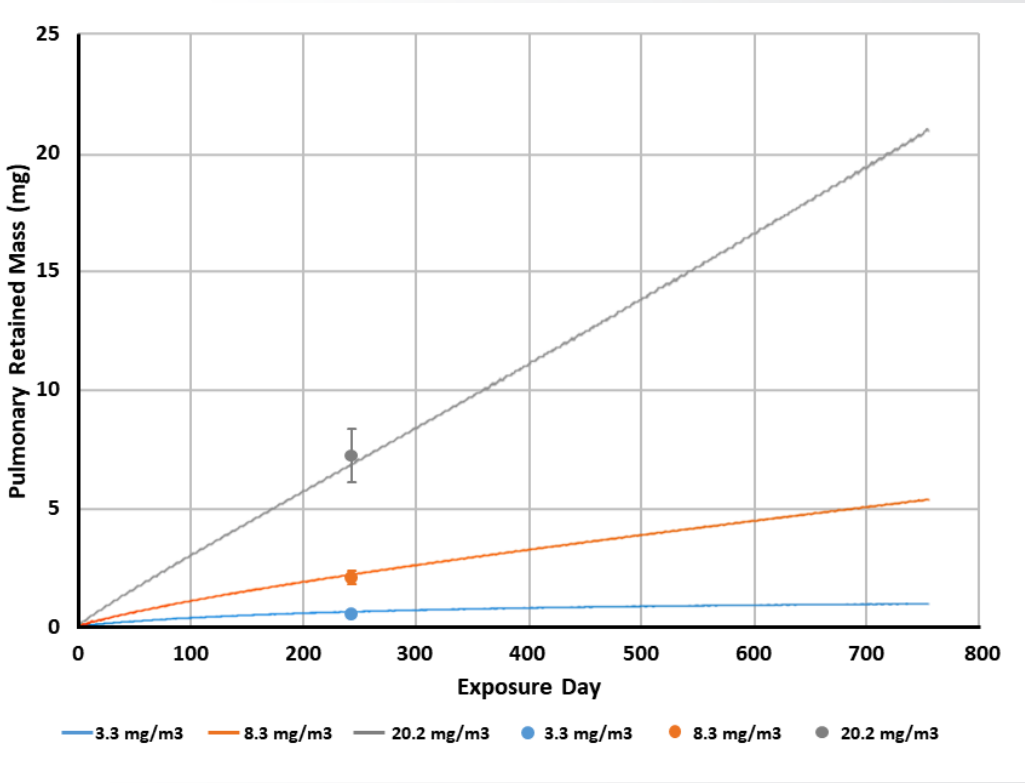
How: Role in Risk Assessment

- Interspecies extrapolation: human equivalent concentration (HEC)
- Improved characterization of target human scenario
  - Specific size, distribution, density and exposure data
  - Replace default parameters and equations



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)



Jarabek, Stedeford et al. (*accepted*)

- **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. Jarabek*[1], *T. Stedeford*[2], *G. S. Ladics*[3], O. T. Price[4], *A. Tveit*[5], M. P. Hayes[6], R. T. Tremblay[7], *S. A. Snyder*[8], K. D. Salazar[2], S. Osman-Sypher[9], *W.Irwin*[2], M. Odin[10], *J. Melia*[10], *H. Carlson-Lynch*[10], *M. Sharma*[11], *A. J. Clippinger*[11], A. O. Stucki[11], and *T. R. Henry*[2]. [1]US EPA, Research Triangle Park, NC; [2]US EPA,Washington, DC; [3]Dupont Nutrition and Biosciences, Wilmington, DE; [4]Applied Research Associates Inc., Arlington, VA; [5]BASF Corporation, Florham Park, NJ;[6]Procter & Gamble, Mason, OH; [7]Procter & Gamble, Strombeek-Beaver, Belgium; [8]Covestro LLC, Pittsburgh, PA; [9]American Chemistry Council, Washington, DC;[10]SRC Inc., North Syracuse, NY; and [11]PETA 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. Henry*[1], K. D. Salazar[1], M. P. Hayes[2], W. Kennedy[3], *A. M. Keene*[3], *A. M. Jarabek*[4], O. T. Price[5], S. Moors[6], *L. Jovanovich*[7], J. L. Rose[8], *A. Tveit*[9], R. T.Tremblay[10], *R. A. Becker*[11], S. Osman-Sypher[11], *P. D. McMullen*[12], *S. D. Slattery*[12], *W. Irwin*[1], M. Odin[13], *J. Melia*[13], *M. Sharma*[14], *A. J. Clippinger*[14], A. Stucki[14], and *T.Stedeford*[1]. [1]US EPA, Washington, DC; [2]Procter & Gamble, St. Bernard, OH; [3]Afton Chemical Corporation, Richmond, VA; [4]US EPA, Research Triangle Park, NC;[5]Applied Research Associates, Inc., Arlington, VA; [6]BASF Corporation, Duesseldorf, Germany; [7]Stepan Company, Northfield, IL; [8]Procter & Gamble, Mason, OH;[9]BASF Corporation, Florham Park, NJ; [10]Procter & Gamble, Strombeek-Beaver, Belgium; [11]American Chemistry Council, Washington, DC; [12]ScitoVation, Durham,NC; [13]SRC Inc., North Syracuse, NY; and [14]PETA International Science Consortium Ltd., London, United Kingdom.

Rollout: Risk Assessment Training

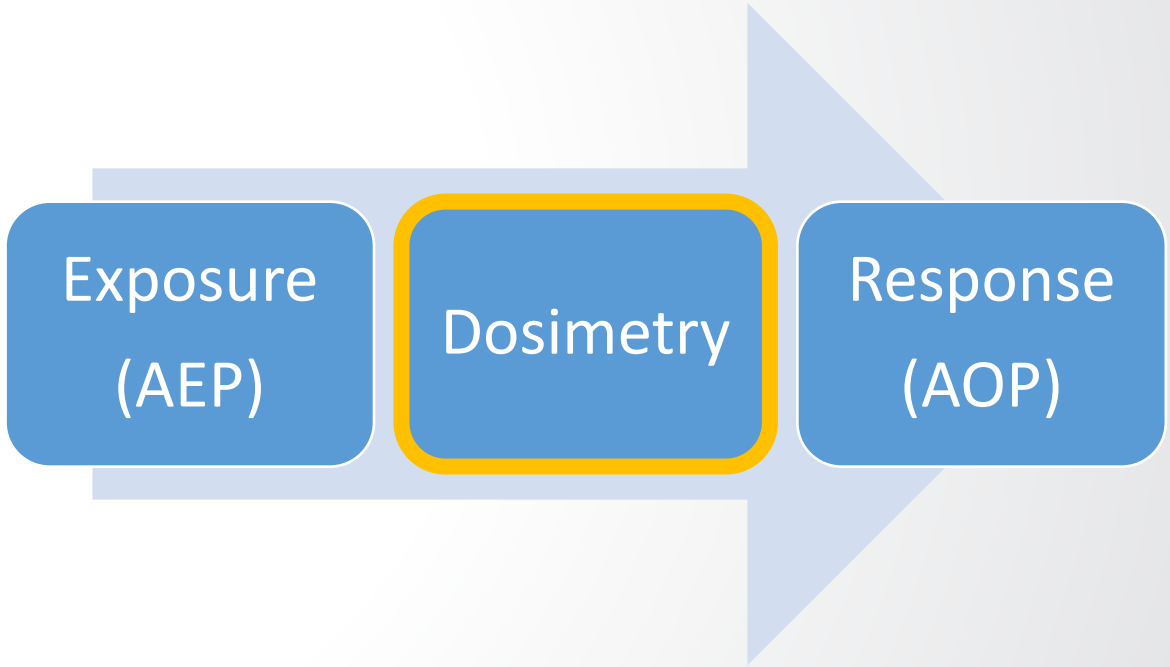
- Didactic and experiential modules with experts to convey scientific subject matter and methodologies
- Collaboration with OCSPP to update for TSCA applications
- MPPD training will be one module within a set covering inhalation issues:
  - Inhalation toxicology
  - Inhalation dosimetry modeling (both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

When: Next Steps

- Release of external peer review document: March 2021
- Virtual public comment and peer review meeting: April 2021
- Revision based on peer panel recommendations: Fall 2021
- Development and deployment of training: Spring 2021
- On-going maintenance and support as part of HERA program
- Build workbench to integrate dosimetry into assessment workflows

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



Benchmark Dose Modeling – Bayesian Model Averaging

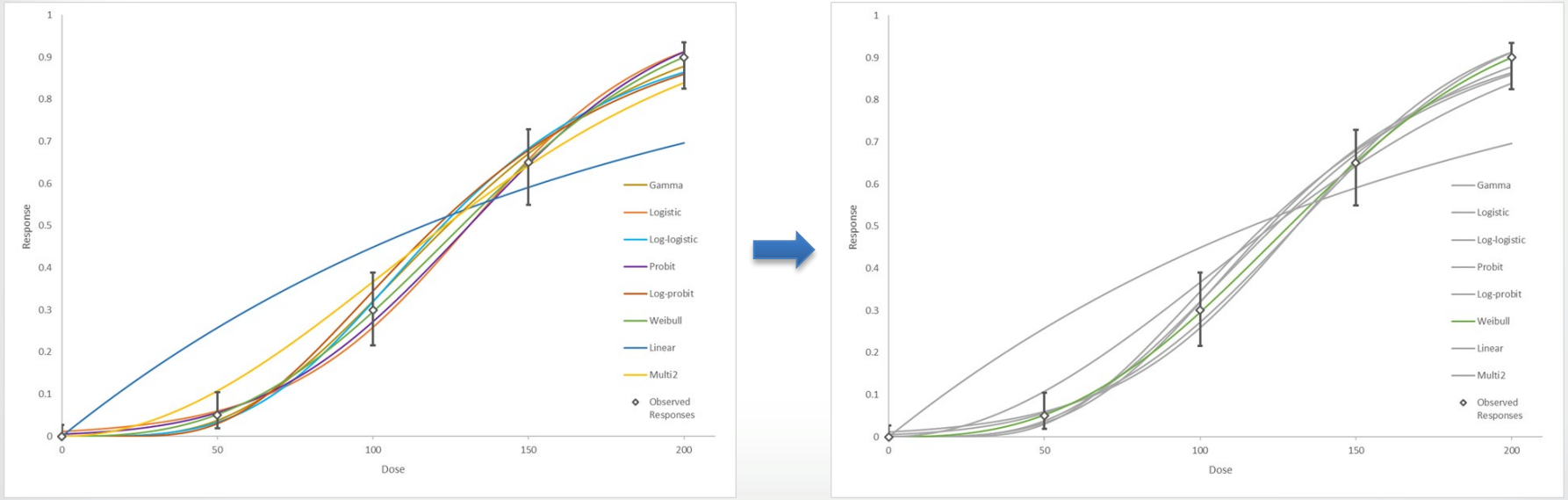
Allen Davis, MSPH

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



Single Model Selection

- **When fitting multiple models to a single dataset, many models can (*and often will*) 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*



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 hyper-flexible
  - ***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
    - 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

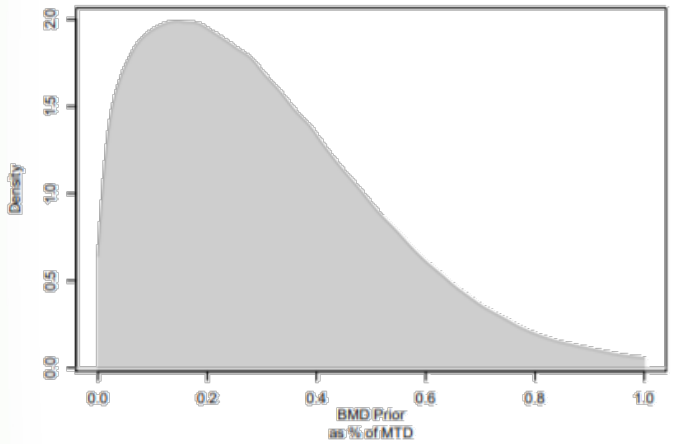
Focused Prior

- **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%)

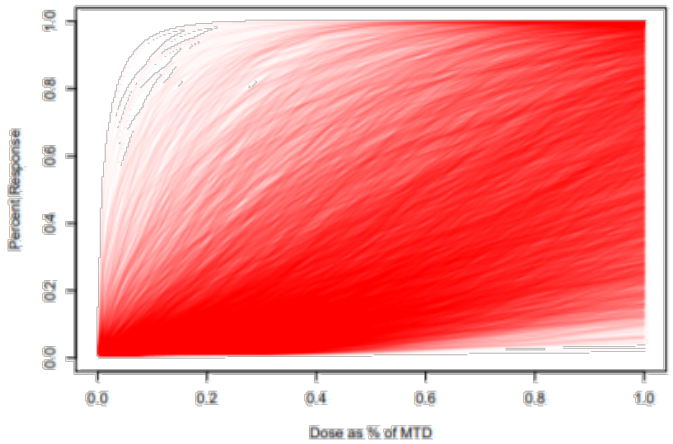
Focused Prior

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

Prior on the BMD



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
- **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**

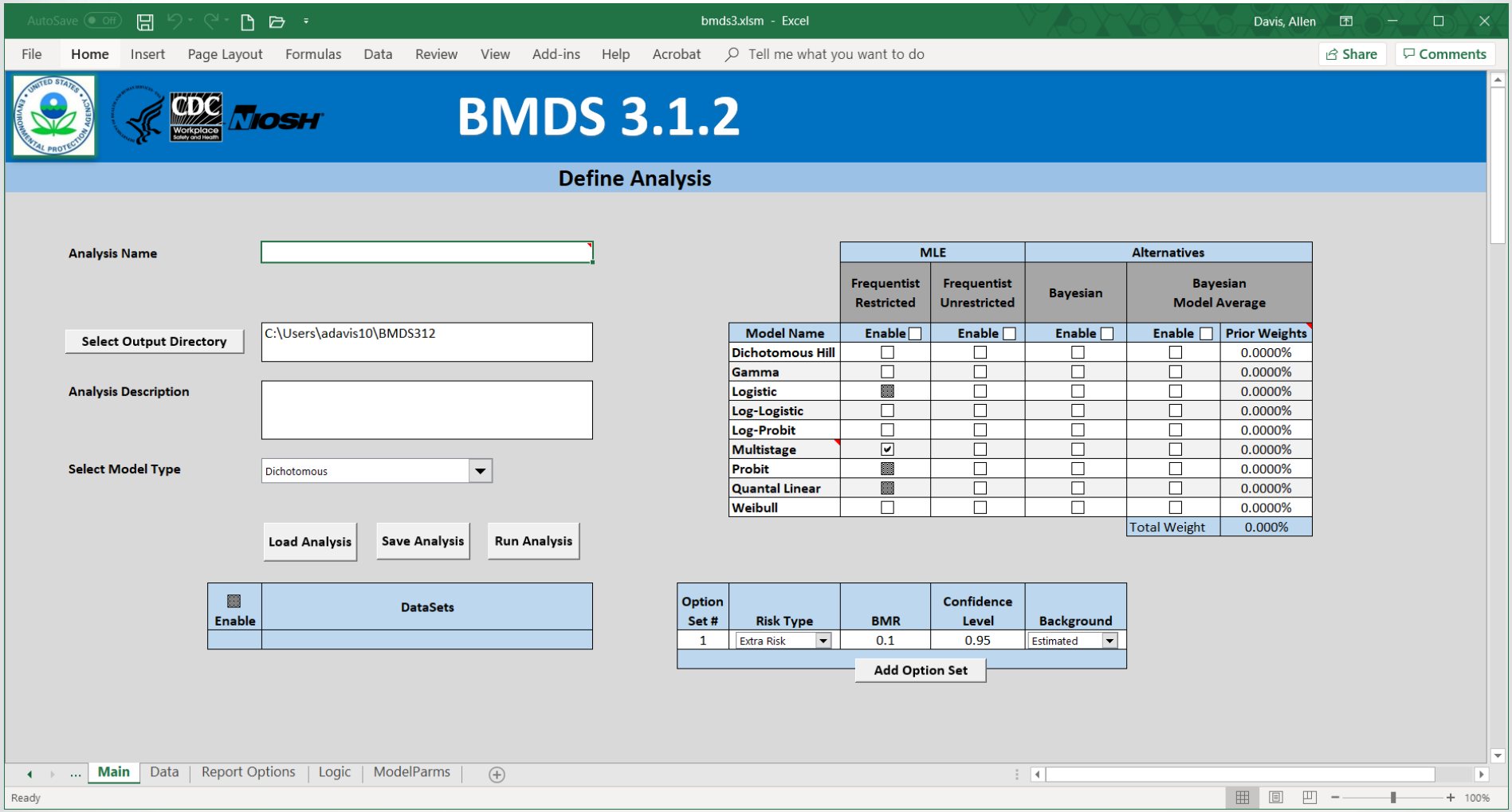
BMDS Bayesian Model Averaging

- **EPA/NIOSH BMA approach was extensively tested against 1) 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**

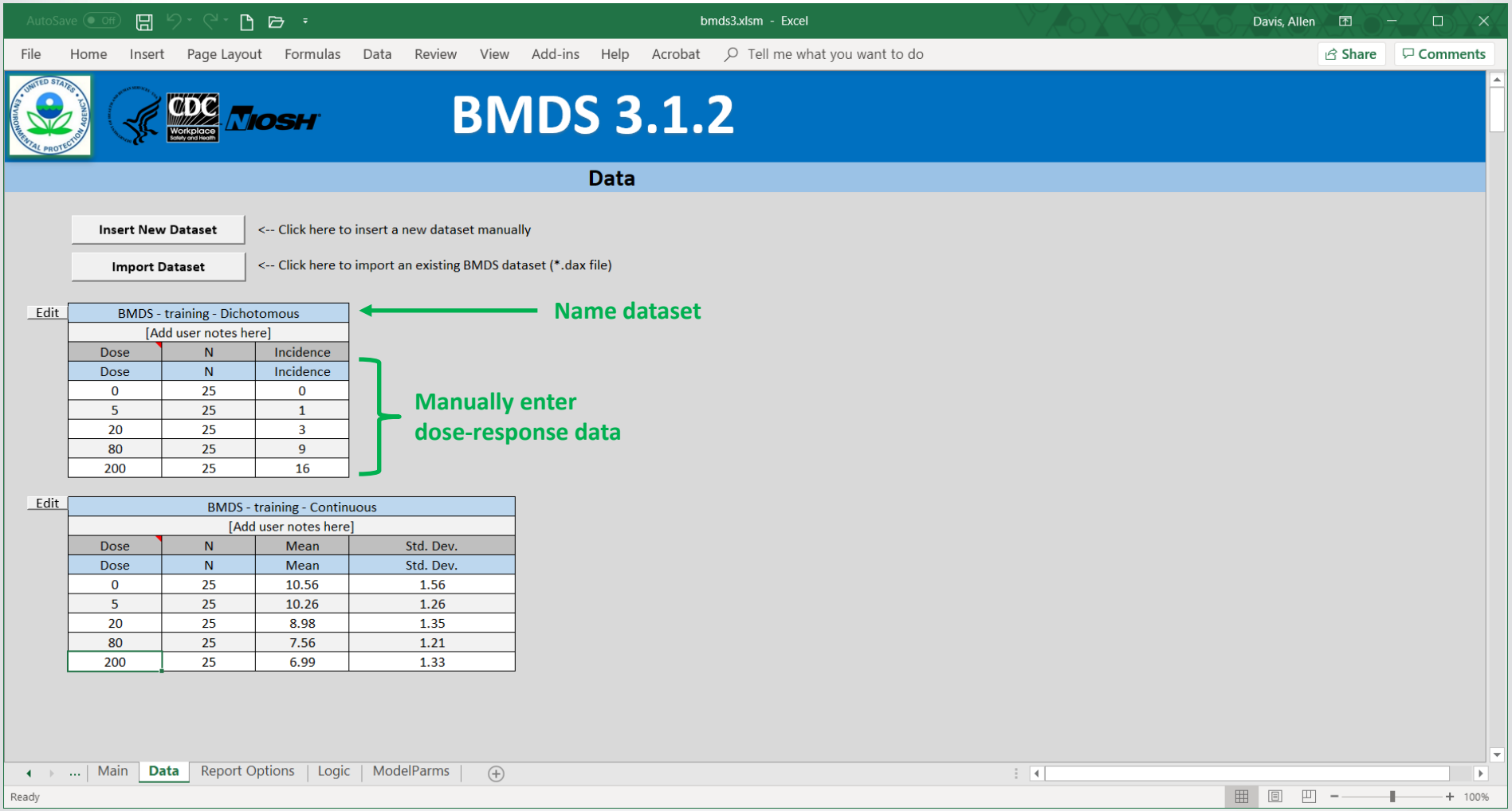
Percentage of Times BMDL Coverage is >90% than True BMD Value

True BMD	BMA	BMDS	NP	MCMC
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%

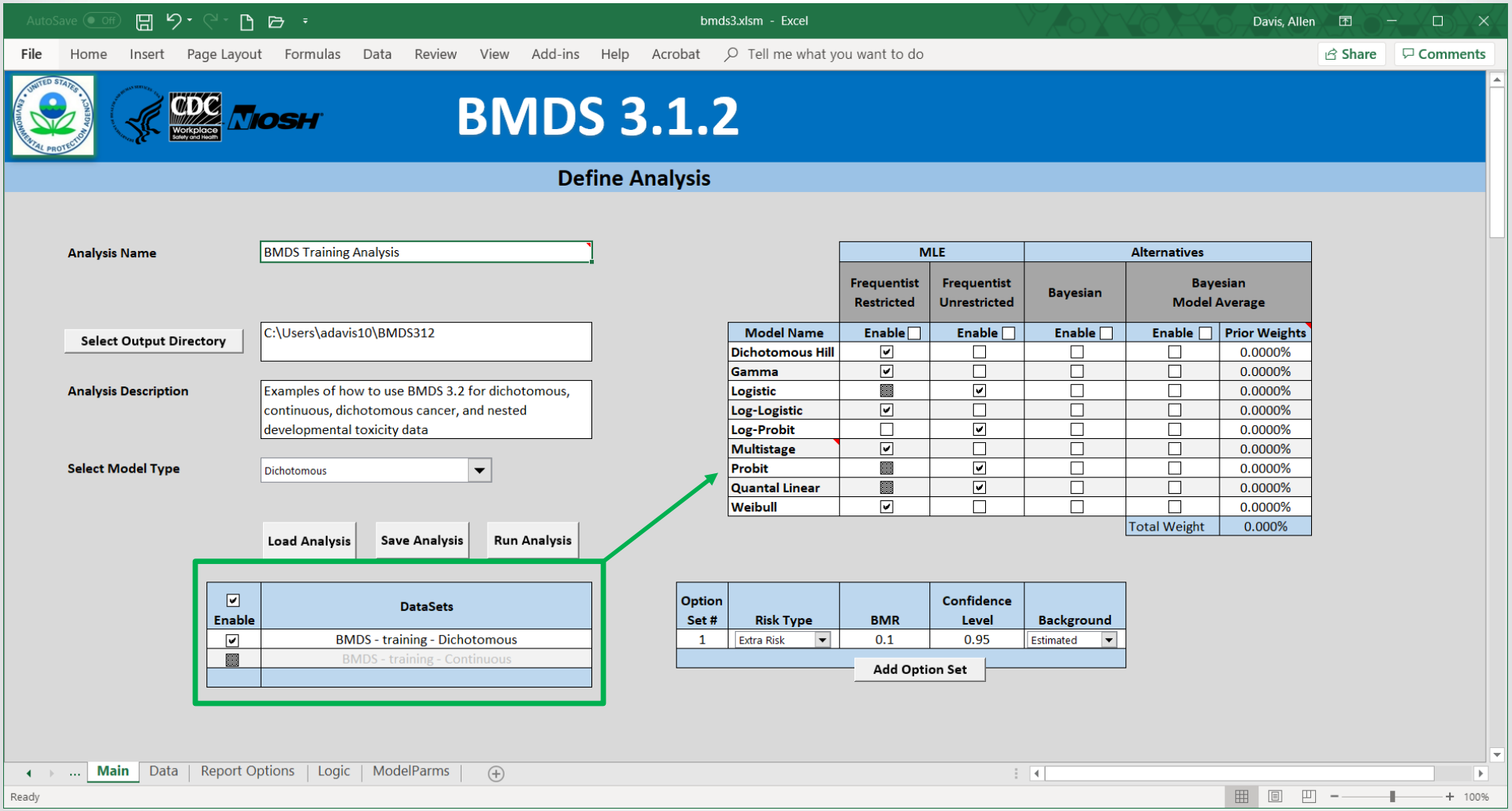
BMDS User Interface



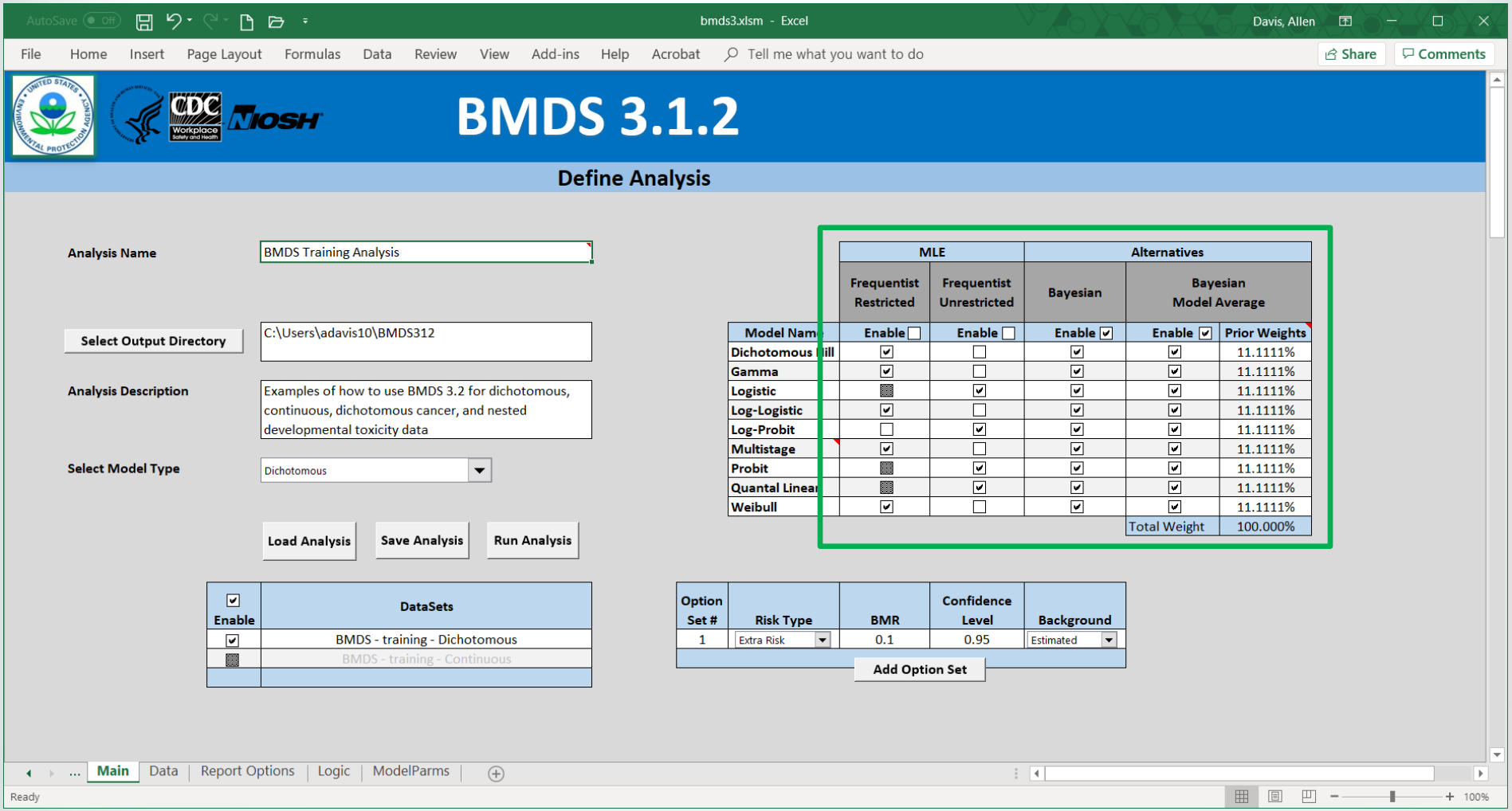
Using BMDS – Enter Dose-Response Data



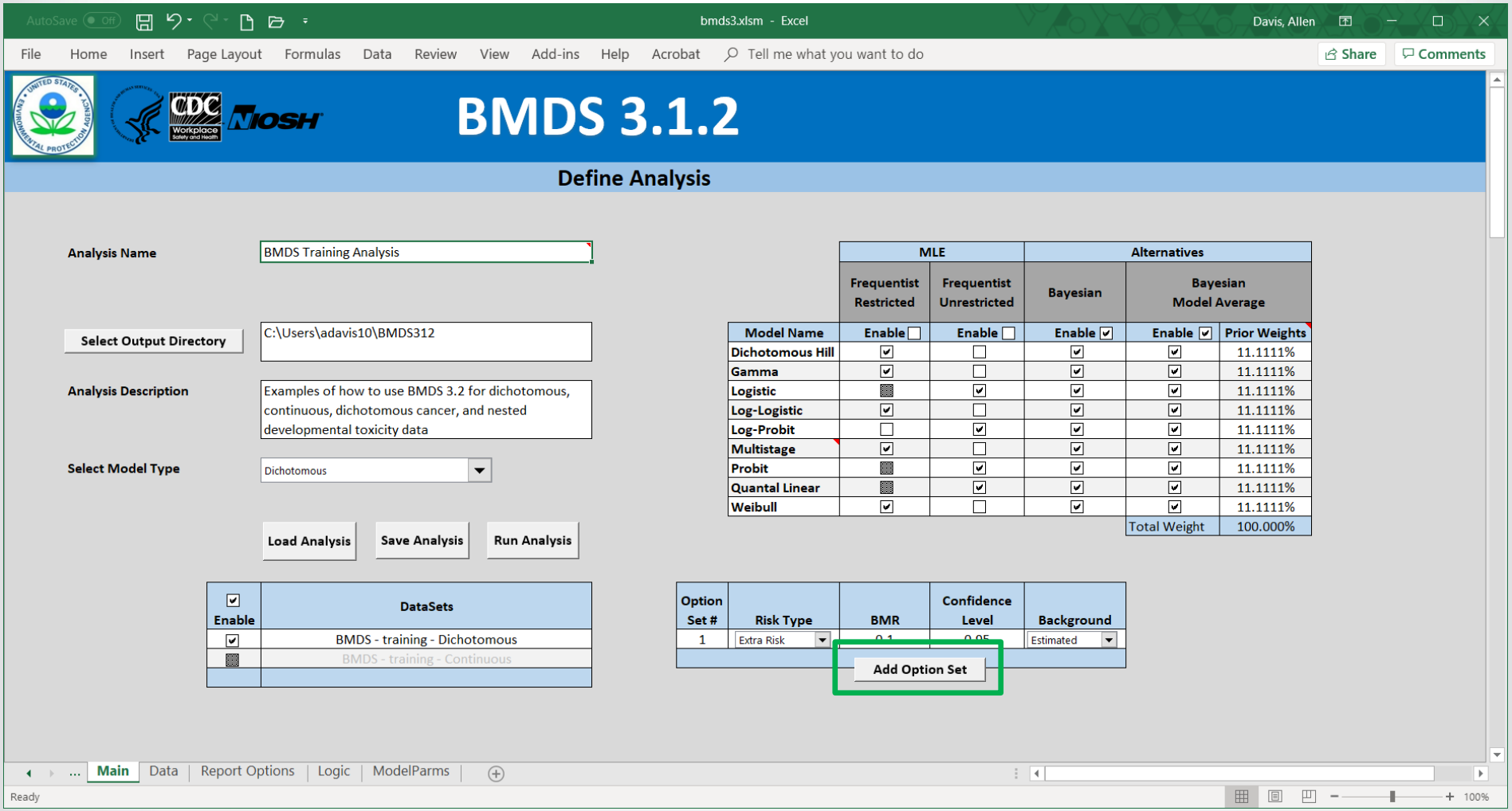
Using BMDS – Select Models to Run



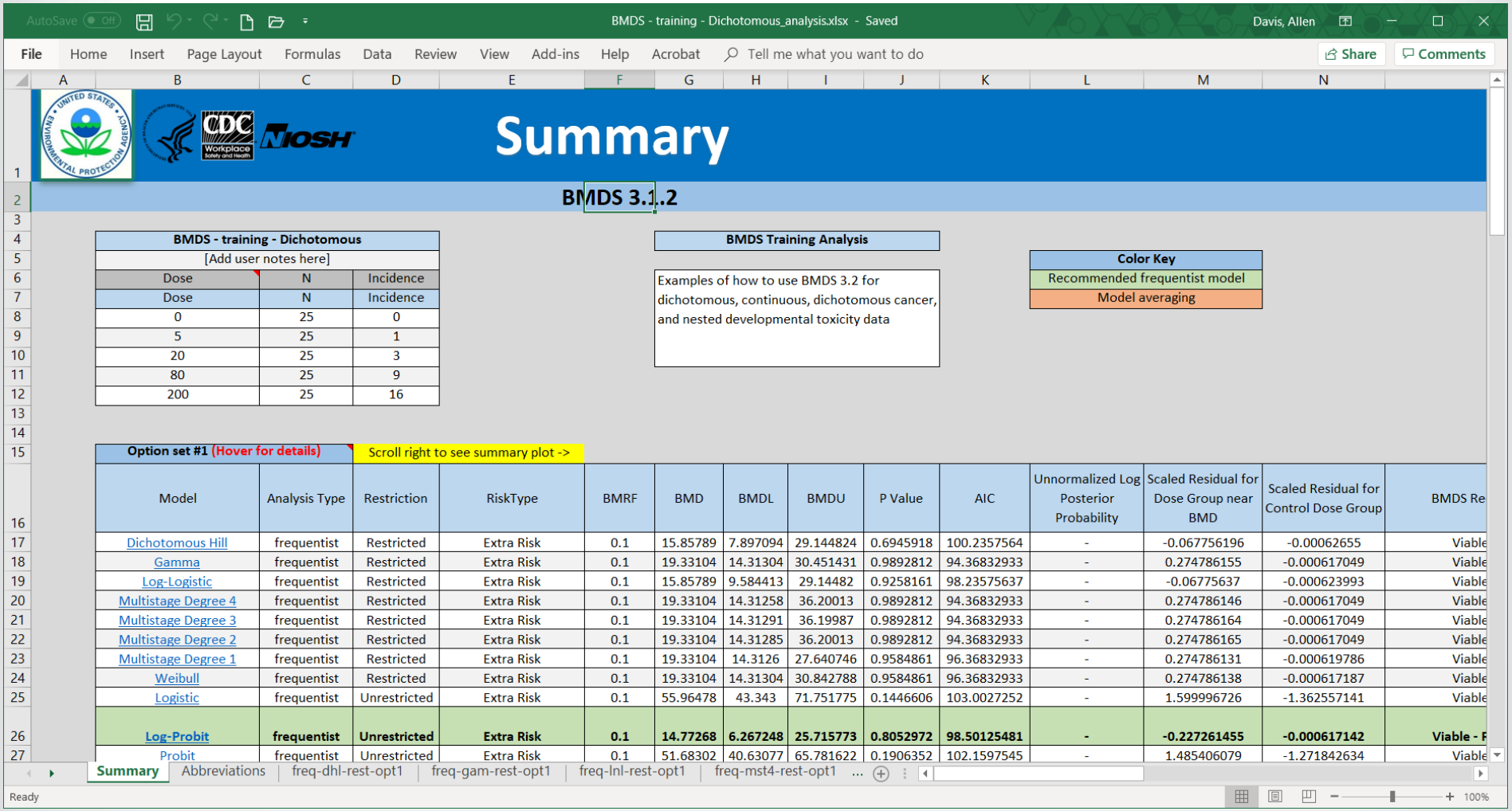
Using BMDS – Select Specific Models



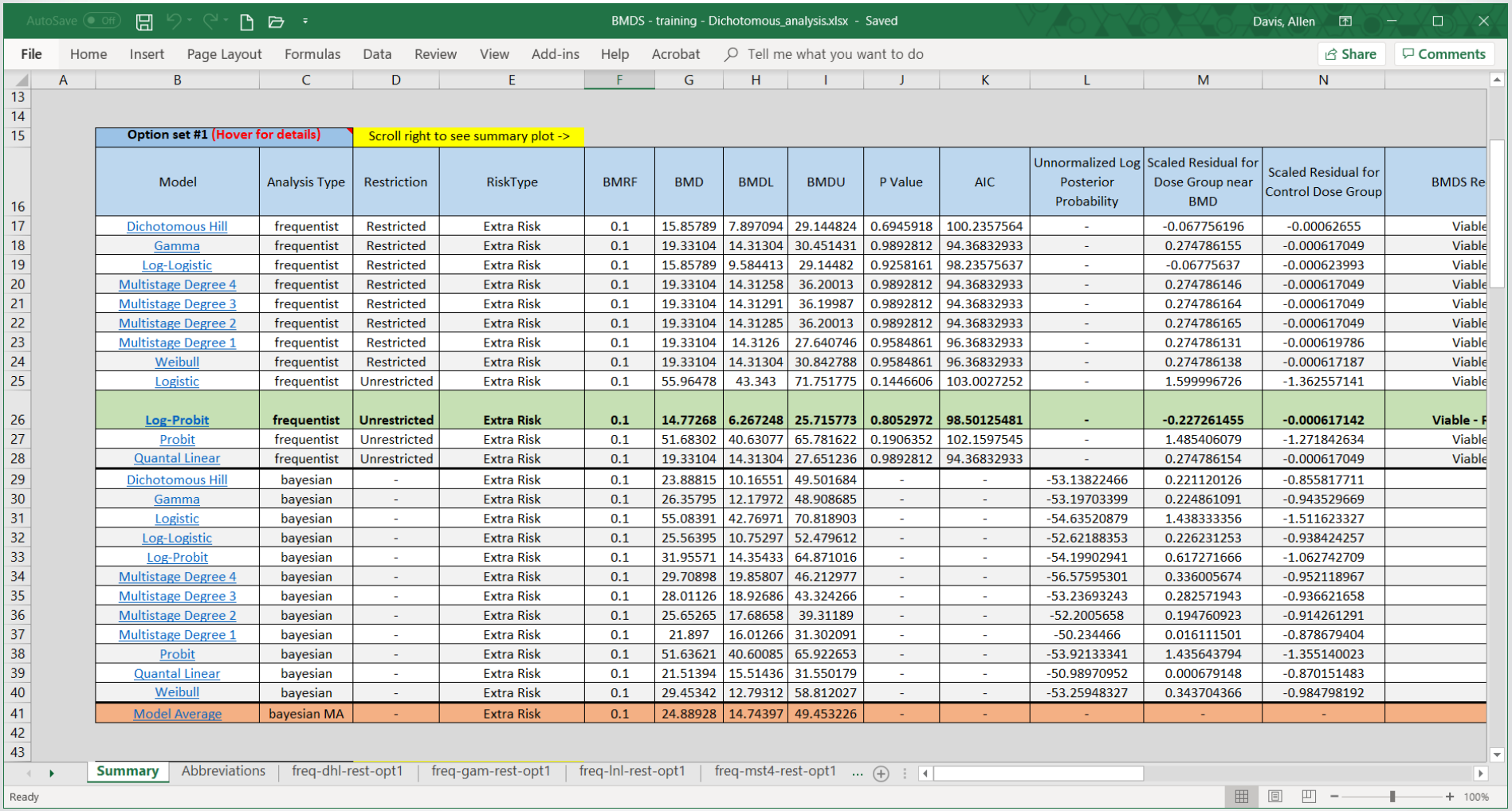
Using BMDS – Add Option Sets



Using BMDS – Modeling Summary Results



Using BMDS – Option Set Results



BMDS - training - Dichotomous_analysis.xlsx - Saved — Davis, Allen

File Home Insert Page Layout Formulas Data Review View Add-ins Help Acrobat Tell me what you want to do — Share — Comments

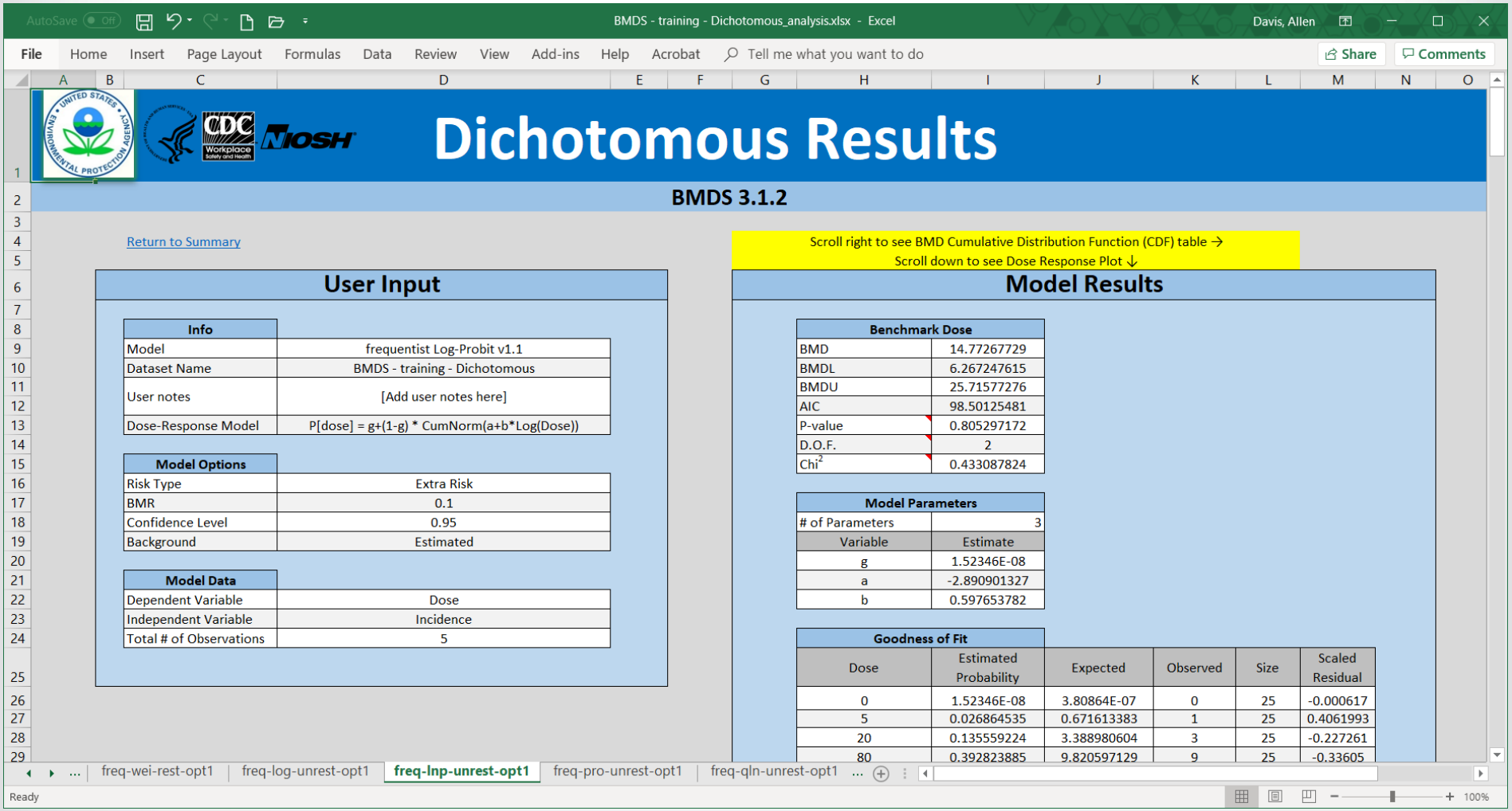
Option set #1 (Hover for details) — Scroll right to see summary plot ->

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
Dichotomous Hill	frequentist	Restricted	Extra Risk	0.1	15.85789	7.897094	29.144824	0.6945918	100.2357564	-	-0.067756196	-0.00062655	Viable
Gamma	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31304	30.451431	0.9892812	94.36832933	-	0.274786155	-0.000617049	Viable
Log-Logistic	frequentist	Restricted	Extra Risk	0.1	15.85789	9.584413	29.14482	0.9258161	98.23575637	-	-0.06775637	-0.000623993	Viable
Multistage Degree 4	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31258	36.20013	0.9892812	94.36832933	-	0.274786146	-0.000617049	Viable
Multistage Degree 3	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31291	36.19987	0.9892812	94.36832933	-	0.274786164	-0.000617049	Viable
Multistage Degree 2	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31285	36.20013	0.9892812	94.36832933	-	0.274786165	-0.000617049	Viable
Multistage Degree 1	frequentist	Restricted	Extra Risk	0.1	19.33104	14.3126	27.640746	0.9584861	96.36832933	-	0.274786131	-0.000619786	Viable
Weibull	frequentist	Restricted	Extra Risk	0.1	19.33104	14.31304	30.842788	0.9584861	96.36832933	-	0.274786138	-0.000617187	Viable
Logistic	frequentist	Unrestricted	Extra Risk	0.1	55.96478	43.343	71.751775	0.1446606	103.0027252	-	1.599996726	-1.362557141	Viable
Log-Probit	**frequentist**	**Unrestricted**	**Extra Risk**	**0.1**	**14.77268**	**6.267248**	**25.715773**	**0.8052972**	**98.50125481**	**-**	**-0.227261455**	**-0.000617142**	**Viable - F**
Probit	frequentist	Unrestricted	Extra Risk	0.1	51.68302	40.63077	65.781622	0.1906352	102.1597545	-	1.485406079	-1.271842634	Viable
Quantal Linear	frequentist	Unrestricted	Extra Risk	0.1	19.33104	14.31304	27.651236	0.9892812	94.36832933	-	0.274786154	-0.000617049	Viable
Dichotomous Hill	bayesian	-	Extra Risk	0.1	23.88815	10.16551	49.501684	-	-	-53.13822466	0.221120126	-0.855817711	
Gamma	bayesian	-	Extra Risk	0.1	26.35795	12.17972	48.908685	-	-	-53.19703399	0.224861091	-0.943529669	
Logistic	bayesian	-	Extra Risk	0.1	55.08391	42.76971	70.818903	-	-	-54.63520879	1.438333356	-1.511623327	
Log-Logistic	bayesian	-	Extra Risk	0.1	25.56395	10.75297	52.479612	-	-	-52.62188353	0.226231253	-0.938424257	
Log-Probit	bayesian	-	Extra Risk	0.1	31.95571	14.35433	64.871016	-	-	-54.19902941	0.617271666	-1.062742709	
Multistage Degree 4	bayesian	-	Extra Risk	0.1	29.70898	19.85807	46.212977	-	-	-56.57595301	0.336005674	-0.952118967	
Multistage Degree 3	bayesian	-	Extra Risk	0.1	28.01126	18.92686	43.324266	-	-	-53.23693243	0.282571943	-0.936621658	
Multistage Degree 2	bayesian	-	Extra Risk	0.1	25.65265	17.68658	39.31189	-	-	-52.2005658	0.194760923	-0.914261291	
Multistage Degree 1	bayesian	-	Extra Risk	0.1	21.897	16.01266	31.302091	-	-	-50.234466	0.016111501	-0.878679404	
Probit	bayesian	-	Extra Risk	0.1	51.63621	40.60085	65.922653	-	-	-53.92133341	1.435643794	-1.355140023	
Quantal Linear	bayesian	-	Extra Risk	0.1	21.51394	15.51436	31.550179	-	-	-50.98970952	0.000679148	-0.870151483	
Weibull	bayesian	-	Extra Risk	0.1	29.45342	12.79312	58.812027	-	-	-53.25948327	0.343704366	-0.984798192	
Model Average	bayesian MA	-	Extra Risk	0.1	24.88928	14.74397	49.453226	-	-	-	-	-	

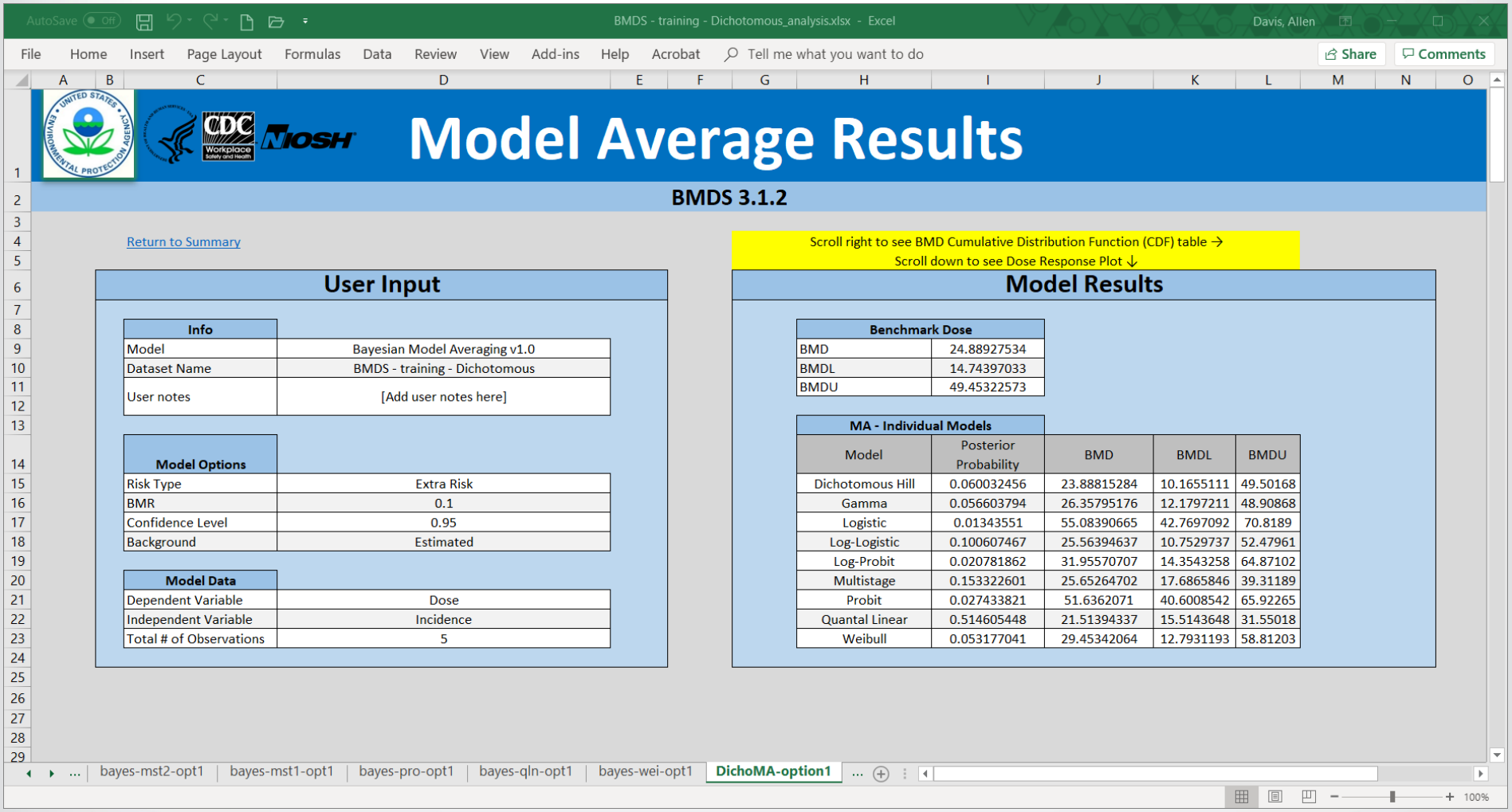
Summary | Abbreviations | freq-dhl-rest-opt1 | freq-gam-rest-opt1 | freq-lnl-rest-opt1 | freq-mst4-rest-opt1 ...

Ready

Using BMDS – Individual Model Results



Using BMDS – Bayesian Model Averaging Results



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

Quantitative Uncertainty Analysis & APROBA

Todd Blessinger, PhD

Center for Public Health and Environmental Assessment
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Presentation at BOSC 2021
February 5, 2021



EPA United States Environmental Protection Agency

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:
  - $\mathrm{RfV} = \frac{\mathrm{POD}}{\mathrm{UF}_1 \times \cdots \times \mathrm{UF}_k}$
  - 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.

- Ex: Endpoint of interest: relative liver weight decrease
  - HD_{05}^{01} = 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

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

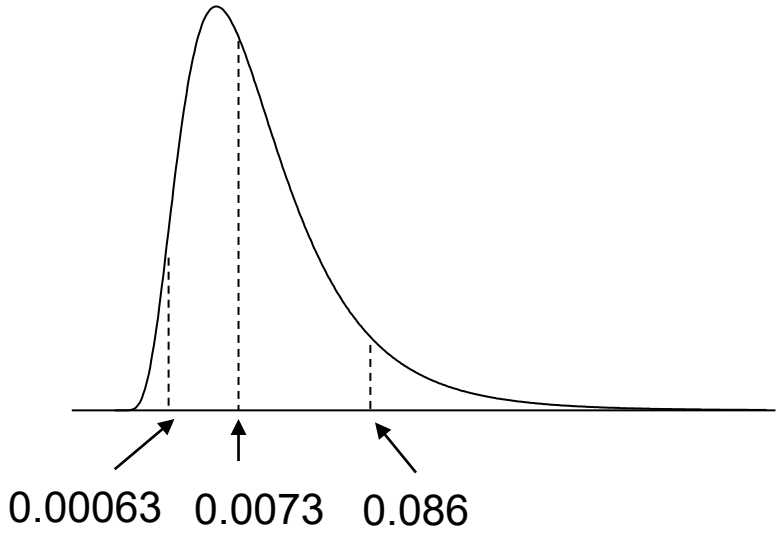
Application of APROBA to acrolein

- 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:

Percentile	Value (mg/m^3)
5th	0.00063
50th (median)	0.0073
95th	0.086



- 5th percentile = 0.00063 mg/m^3 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)
5th	0.0015
50th (median)	0.014
95th	0.133

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Next Steps

- 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.

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Summary & Conclusions

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

Resources

- 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