



HESI.

Quantitative Dose-Response Analyses for Risk Assessment and Regulatory Decision-Making: Issues, Applications, and Challenges

Dr George Johnson
Swansea University Medical School
Chair, HESI-GTTC Quantitative Group

ILSI Health and Environmental Sciences Institute

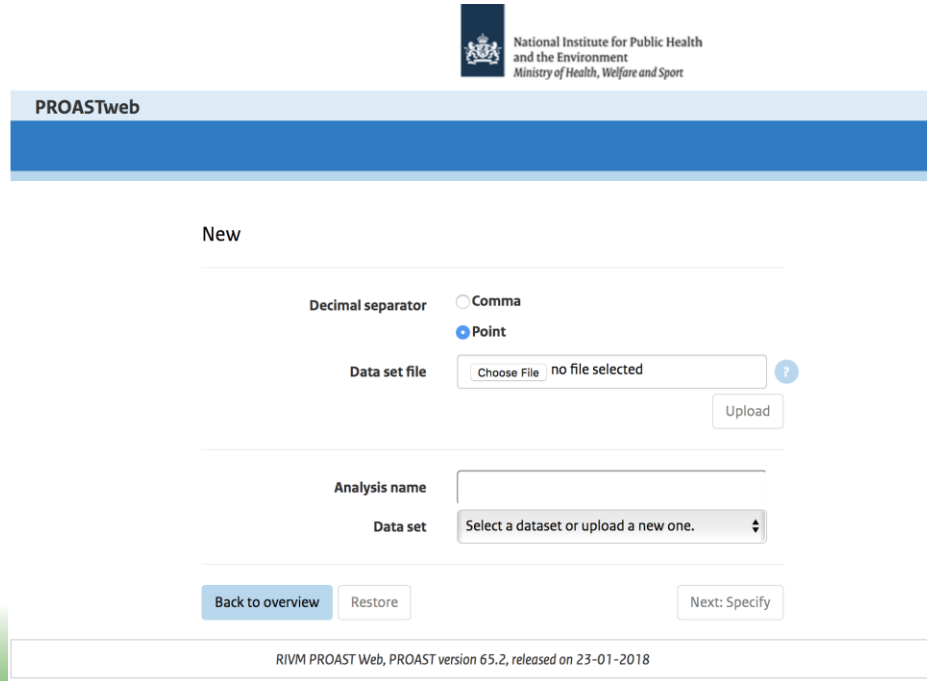
MAIN BENEFITS OF ENDPOINT SPECIFIC CRITICAL EFFECT SIZES (CES) TO THE USERS AND ASSESSORS

1. In line with expert guidance.
2. A default of 10% leads to BMD CI and points of departure (reference doses), that are too low and often lack precision.
3. Moving to a higher position on the graph (10% to 50% above background), takes the BMD estimate to a more precise area of the model, with generally tighter and higher dose BMD CI.
 - As a result, the BMDL is often higher and the BMDL:BMDU ratio is lower.



HOW TO CARRY OUT THE BMD APPROACH?

How to do it? <https://proastweb.rivm.nl>



The screenshot displays the PROASTweb interface. At the top, there is a logo for the National Institute for Public Health and the Environment, Ministry of Health, Welfare and Sport. Below the logo is a blue header bar with the text 'PROASTweb'. The main content area is titled 'New' and contains a form for creating a new analysis. The form includes a 'Decimal separator' section with radio buttons for 'Comma' and 'Point', where 'Point' is selected. Below this is a 'Data set file' section with a file selection button labeled 'Choose File' and the text 'no file selected', followed by an 'Upload' button. The 'Analysis name' section has an empty text input field. The 'Data set' section has a dropdown menu with the text 'Select a dataset or upload a new one.' At the bottom of the form, there are three buttons: 'Back to overview', 'Restore', and 'Next: Specify'. A footer bar at the bottom of the page contains the text 'RIVM PROAST Web, PROAST version 65.2, released on 23-01-2018'.

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

PROASTweb

New

Decimal separator Comma Point

Data set file no file selected

Analysis name

Data set

RIVM PROAST Web, PROAST version 65.2, released on 23-01-2018



Research Article

Quantitative Dose–Response Analysis of Ethyl Methanesulfonate Genotoxicity in Adult *gpt*-delta Transgenic Mice

Xuefei Cao,¹ Roberta A. Mittelstaedt,¹ Mason G. Pearce,¹ Bruce C. Allen,²
Lya G. Soeteman-Hernández,³ George E. Johnson,⁴ C. Anita H. Bigger,⁵
and Robert H. Heflich^{1*}

¹*U.S. Food and Drug Administration, National Center for Toxicological Research, Jefferson, Arkansas*

²*Bruce Allen Consulting, Chapel Hill, North Carolina*

³*Centre for Health Protection, National Institute for Public Health and the Environment, Bilthoven, The Netherlands*

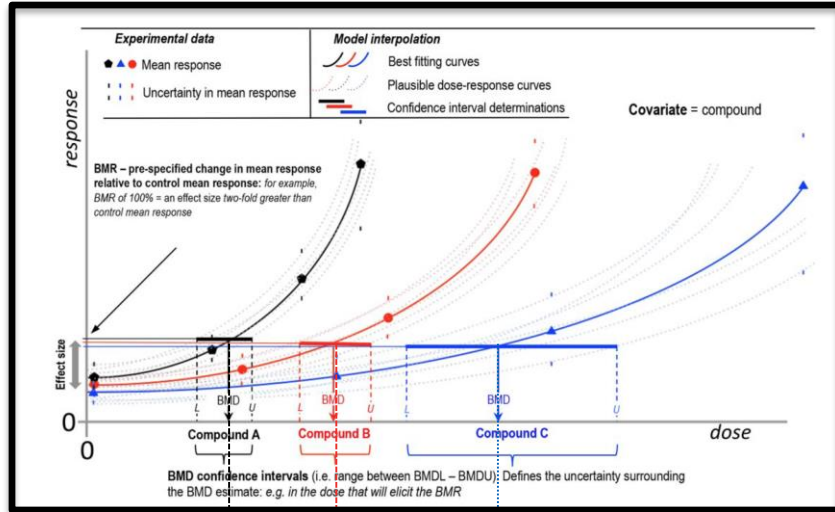
⁴*Institute of Life Science, College of Medicine, Swansea University, Wales, United Kingdom*

⁵*Bigger Consulting, St. Augustine, Florida*

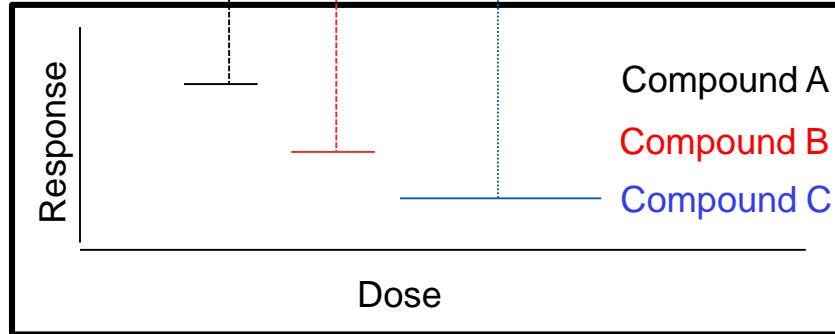


In vivo – covariate analysis to improve BMD analysis

BMD potency ranking



It was assumed that the maximum response and log-steepness were equal for all response curves, while parameters for background response, potency and within group variation were examined for being covariate dependent (Slob and Setzer 2014).



TDI/AI: Tolerable/Acceptable Daily Intake

1. *In Vivo* BMD Confidence interval (CI)
2. Allometric Scaling Factor (FDA, 2005) = **0.16** for rat **0.081** mouse
3. **Human-equivalent dose**, assuming e.g. 60kg
4. Overall Assessment **Factor**
10 inter-individual x 10 effect severity x others? = **100** or other?

Tolerable/Acceptable Daily Intake (**TDI/ADI**) Estimate

$$\text{TDI/ADI} = \frac{(\text{BMD CI}) * (\text{Allometric SF}) * (\text{Human equiv. dose})}{\text{Assessment factors}}$$



ETOPOSIDE



Mutation Research 342 (1995) 71–76



The in vivo rat micronucleus test: integration with a 14-day study

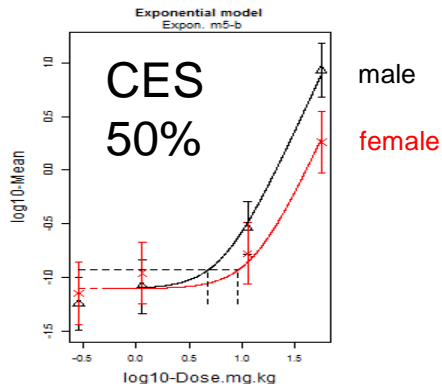
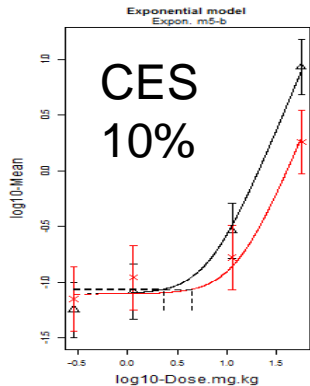
Michael L. Garriott *, Jamie D. Brunny, Delinda E.F. Kindig, Joseph W. Parton,
Linda S. Schwier

Lilly Research Laboratories, A Division of Eli Lilly and Company, Greenfield, IN 46140 USA

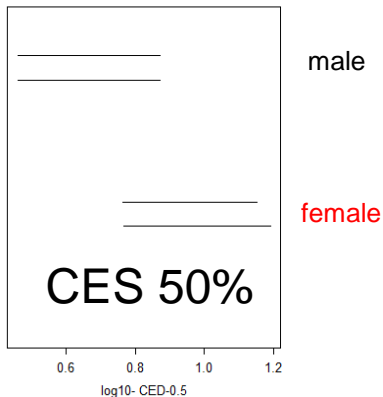
Received 13 June 1994; revised 2 November 1994; accepted 28 November 1994



ETOPOPOSIDE



BMD confidence intervals
(exponential and Hill, per subgroup)



Covariate.	MN PCE%
	male
BMDL₁₀ (mg/kg) (CES 10%)	1.16
BMDU₁₀ (mg/kg) (CES 10%)	3.97
BMDL₅₀ (mg/kg) (CES 50%)	2.89
BMDU₅₀ (mg/kg) (CES 50%)	7.42
Adjustment Factors	100
Allometric Scaling	0.16
Person.kg	60
AI.L (mg/kg/person) (CES 10%)	0.11
AI.U (mg/kg/person) (CES10%)	0.38
AI.L (mg/kg/person) (CES 50%)	0.28
AI.U (mg/kg/person) (CES 50%)	0.71



FINAL POINTS

1. CES 10% vs 50%
2. Assessment factors bigger influence than CES %
3. Covariate BMD can be used to improve the analysis
4. Adjusting study design to capture parameter/variable e.g. genetic diversity (DO), can provide more precise BMD CI as well as potentially influence the assessment factors used thereafter.
5. Once BMD CI have been defined for each chemical, mode of action information can be used to help select adjustment factors.





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END

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