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

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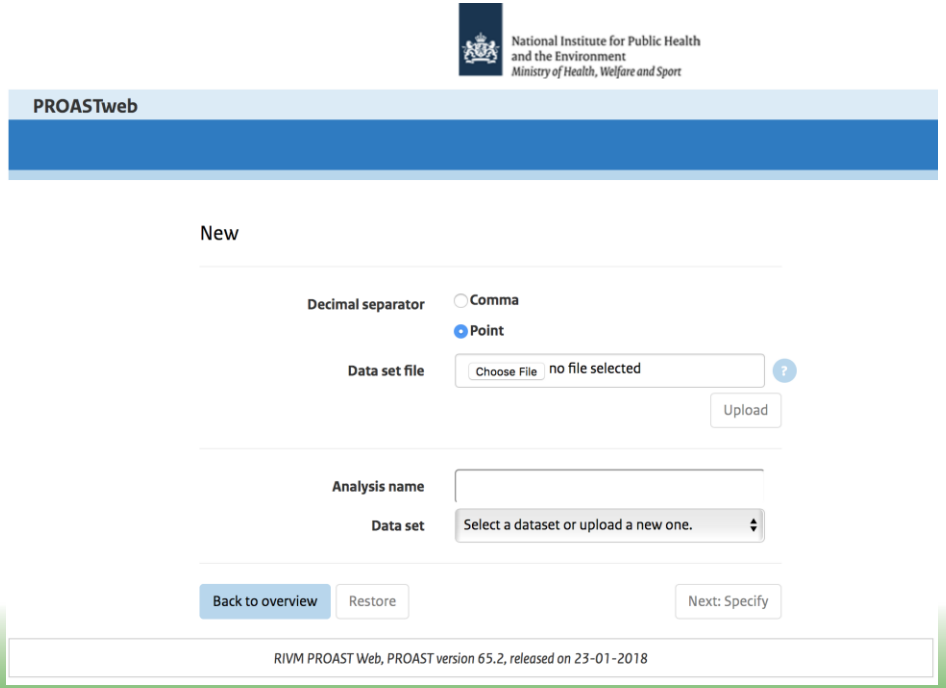
MAIN BENEFITS OF ENDPOINT SPECIFIC CRITICAL EFFECT SIZES (CES) TO THE USERS AND ASSESSORS

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



Environmental and Molecular Mutagenesis 55:385–399 (2014)

Research Article

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

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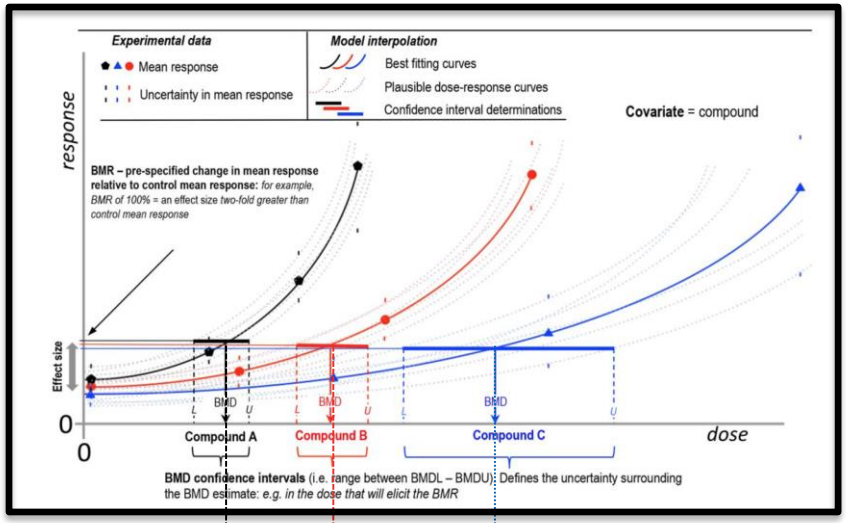
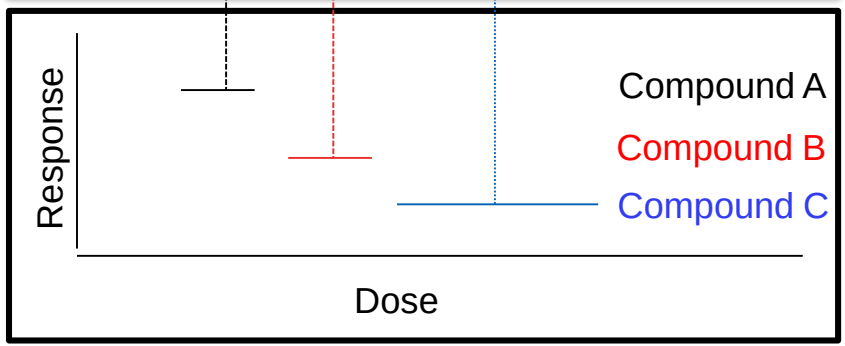
In vivo – covariate analysis to improve BMD analysis

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

ELSEVIER

Mutation Research 342 (1995) 71–76

Genetic Toxicology

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

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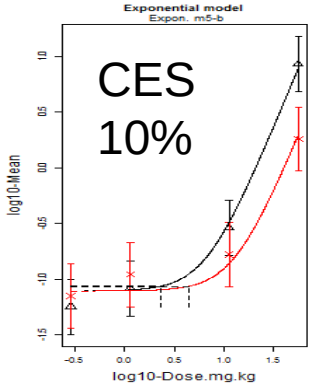
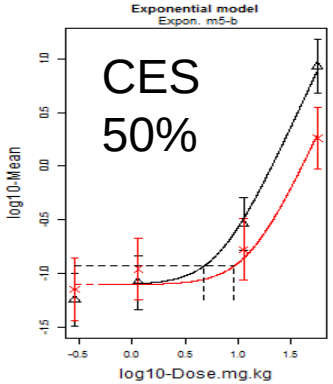
Received 13 June 1994; revised 2 November 1994; accepted 28 November 1994

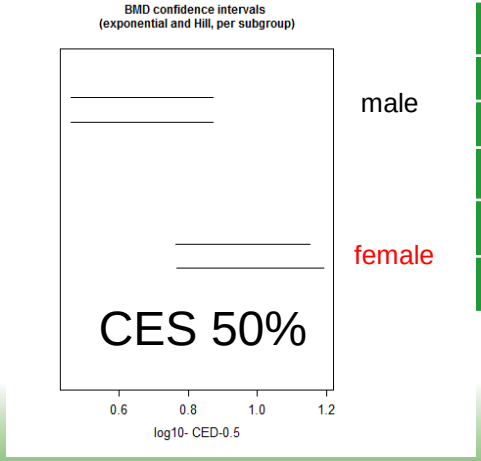
ETOPOSIDE





male

female



male

female

Covariate.	MN PCE%
	male
$BMDL_{10}$ (mg/kg) (CES 10%)	1.16
$BMDU_{10}$ (mg/kg) (CES 10%)	3.97
$BMDL_{50}$ (mg/kg) (CES 50%)	2.89
$BMDU_{50}$ (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.

END