IGG considerations and AZ case study

Practical experiences with BMD data

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AstraZeneca

Industrial experience with BMD PoD

Pharma limited examples
And a few concerns

Unilever Quercetin

Syngeneta

IGG meetings
Since 2011

In vitro extrapolation focus

Pathways approaches, in theory

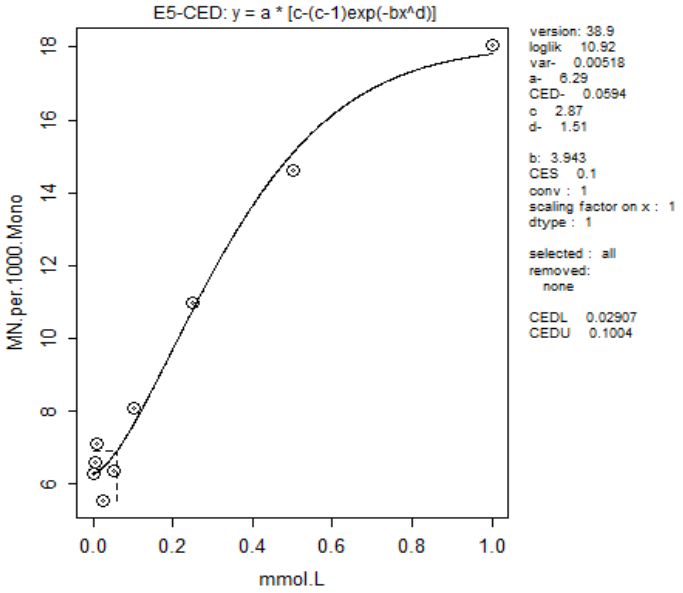
Workshops and case studies
Lead by Unilever eg Quercetin

AZ aneugen series compounds in vitro and in vivo data

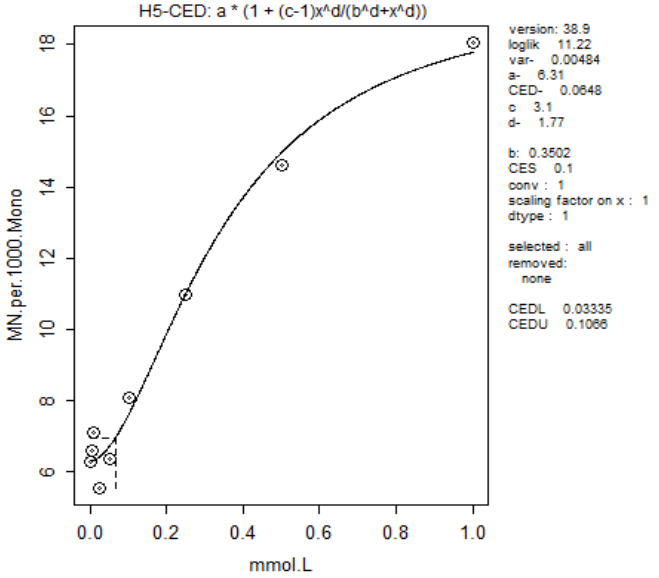
In vitro Mn data for AZ4

AZ4 TK6 data models well

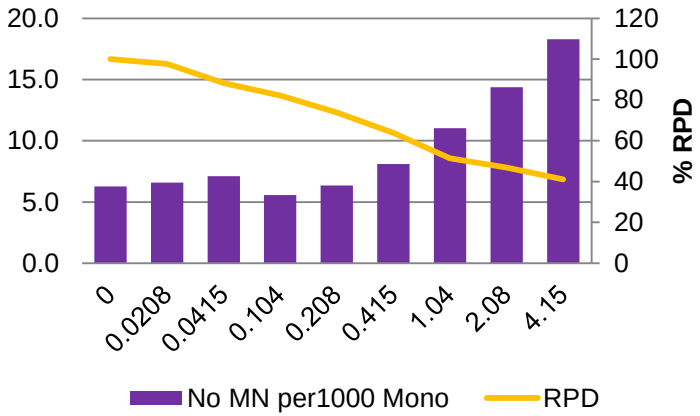
Exponential model



Hill model



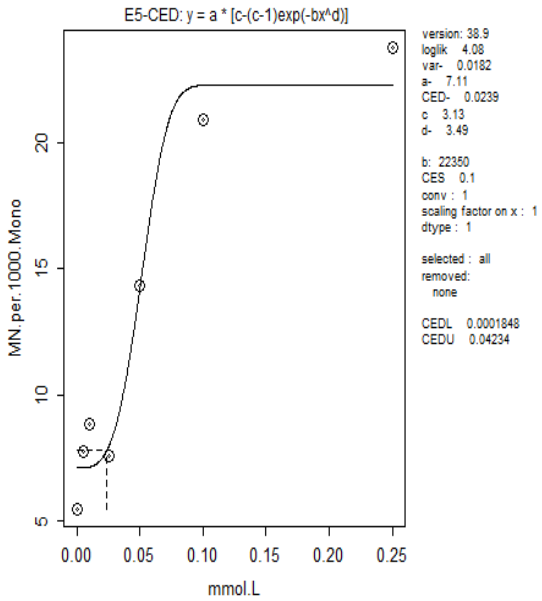
The lowest BMDL and highest BMDU from exponential and Hill models are:0.0291 and 0.1066

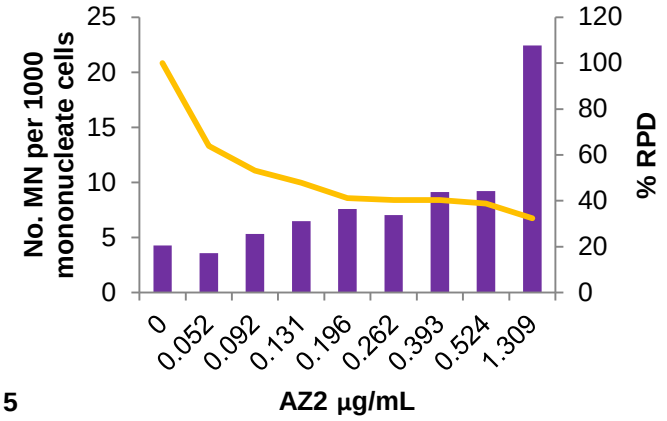


In vitro Mn data for AZ3

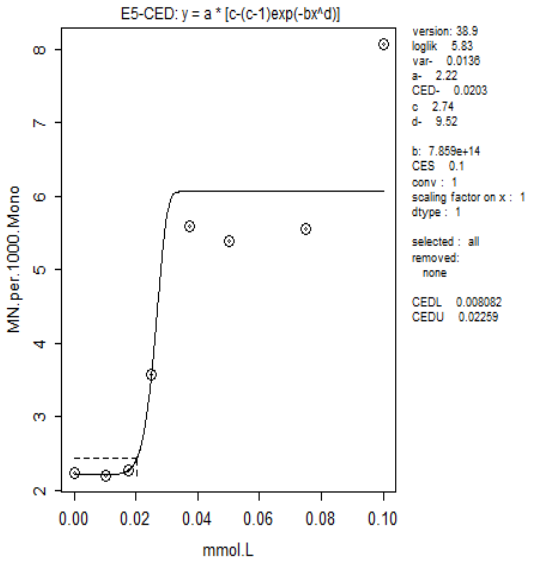
7990 TK6 & L5 data exponential data (Hill wouldn't model)

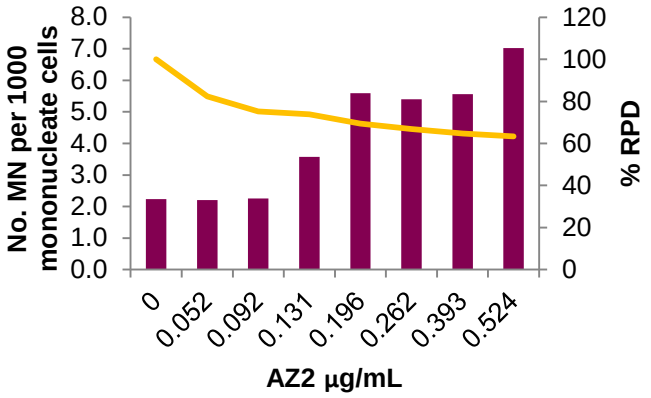
TK6





L5178Y

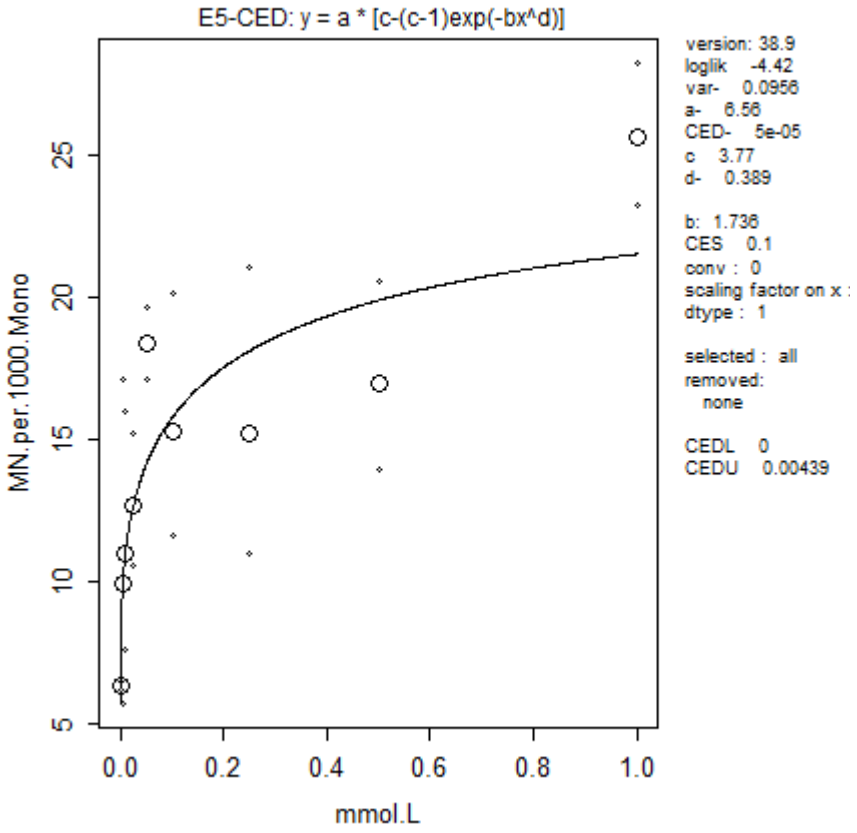




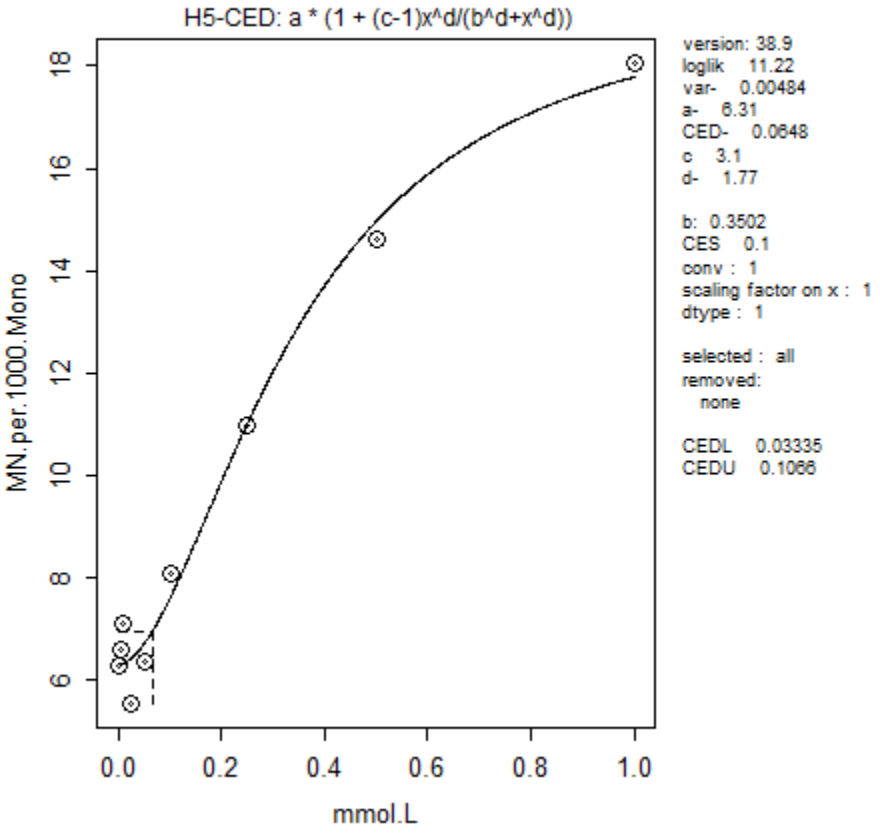
In vitro Mn data for AZ1

AZ1 TK6 data

Exponential model

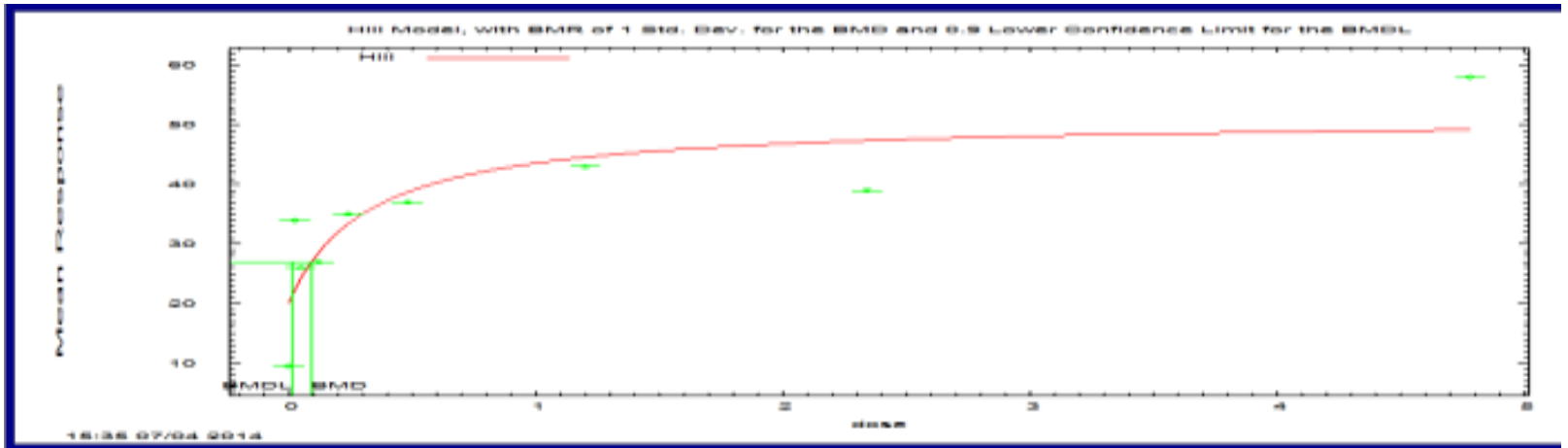


Hill model



The lowest BMDL and highest BMDU from exponential and Hill models are:0 and 0.0071

EMA Hill data PF AZ1



C:\Users\paul.fowler\Google Drive\BMDS\BMD 10 calculations\benzo a pyrene\hill_benzo a pyrene_Opt.out

responses.D The user may wish to consult a statistician if this
issue is seen or suspected.

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

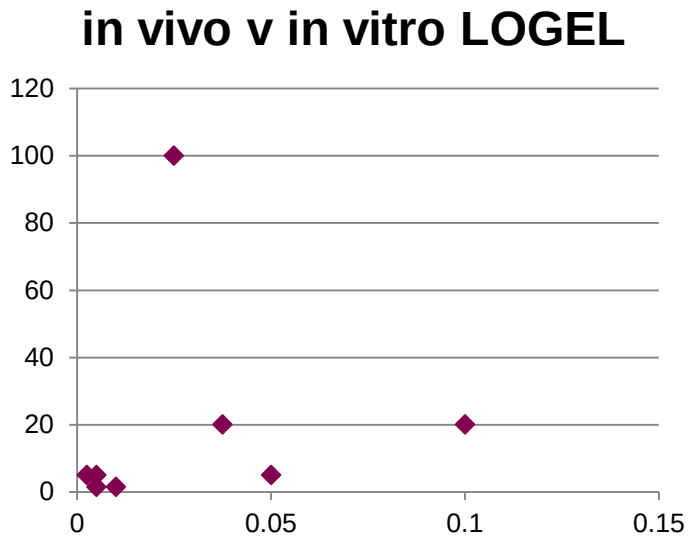
Confidence level = 0.9

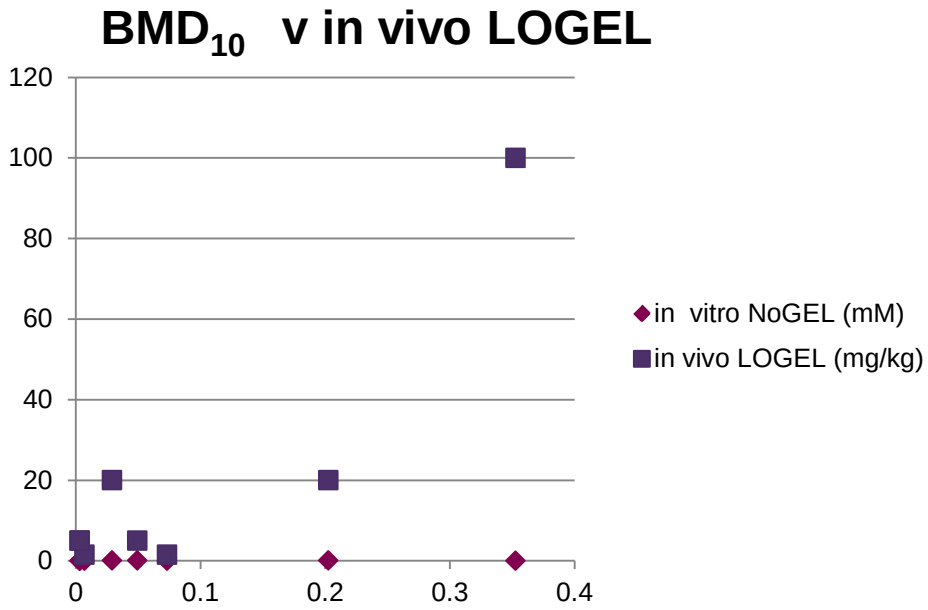
BMD = 0.0902448

BMDL = 0.014673

AZ data examples

Aneugenic series compounds





Questions to this group

Would we expect series with similar potency at target similar MOA be expected to give pattern in BMD data?

Now many dose points do we need to BMD in vivo data?

Can comparison be mixed in vitro BMD to LOGEL on in vivo?

Should PoD have been done instead of BMD as we know series has aneugenic MOA

Are we biasing data sets as we select what to score in vitro based on cell counts

How does toxicity affect BMD calculations?

Thanks

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IGG
Paul Fowler Unilever
Ewan Booth Syngenta
Mick Fellows AZ