Use of epidemiological studies for setting a health-based guidance value

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Setting health based guidance values (HBGV)

Hazard characterization:

- Identifying critical outcomes and studies.
- Determine point of departure …
- ..preferably by using bench mark dose analyses
- **Can the same methodology be used for human observational studies?**

Controlled animal experiments
why use something else?

- The controlled setting is major strength that cannot be matched by human observational studies (when studying potential adverse effects)
- More time and cost effective than large scale epidemiological studies
- Subject to far fewer ethical constraints

Controlled animal experiments
why use something else?

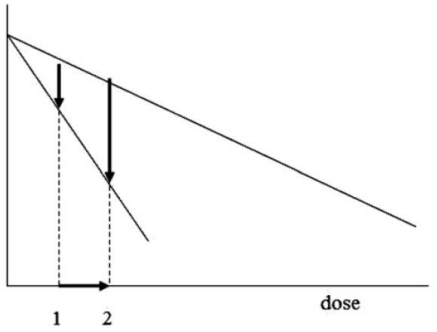
- The controlled setting is major strength that cannot be matched by human observational studies (when studying potential adverse effects)
- More time and cost effective than large scale epidemiological studies
- Subject to far fewer ethical constraints……**but**

≠

HBGV: critical outcomes and critical studies

- The luxury of working with controlled studies often results in large weights being given to one study
  - ….most critical outcome
  - ….**most critical study**

- The study population and the environment partly determines the dose response



Determining point of departure

BMD

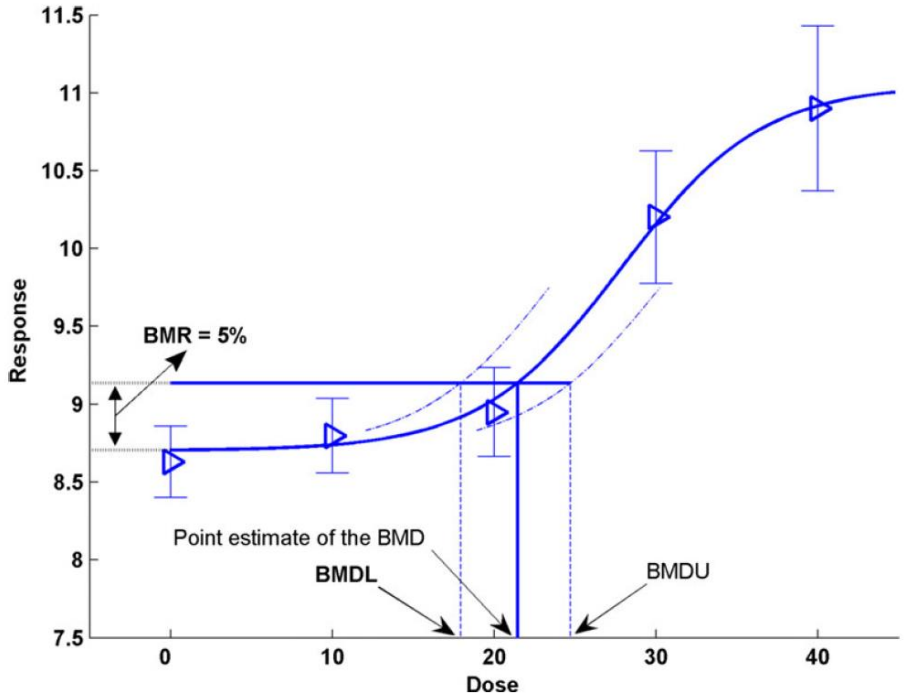
NOAEL

GUIDANCE?

≠

Bench Mark Dose (BMD)

- More precise in determining POD than use of NOAEL
- Takes biological relevance into considerations
- The model fit provides some information on
  - study quality
  - uncertainty
  - and biological plausibility



EFSA guidance

GUIDANCE

EFSA Journal

ADOPTED: 17 November 2016

doi: 10.2903/j.efsa.2017.4658

Update: use of the benchmark dose approach in risk assessment

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger,
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EFSA guidance

- Maximum likelihood
- Model averaging for quantile data
- Restricted set of models
- **The continuous models are not conventionally used in human epidemiology**

Model	Number of model parameters	Model expression mean response (y) as function of dose (x)
Quantal data		
Logistic	2	$y = 1/(1 + \exp(-a-bx))$
Probit	2	$y = \text{CumNorm}(a + bx)$
Log-logistic	3	$y = a + (1-a)/(1 + \exp(-\log(x/b)/c))$
Log-probit	3	$y = a + (1-a)\ \text{CumNorm}(\log(x/b)/c)$
Weibull	3	$y = a + (1-a)\ \exp((x/b)^c)$
Gamma	3	$y = a + (1-a)\ \text{CumGam}(bx^c)$
LMS (two-stage) model	3	$y = a + (1-a)(1-\exp(-bx-cx^2))$
Latent variable models	Depends on	These models assume an underlying
Continuous data		
Exponential family		
3-parameter model[iii]	3	$y = a\ \exp(bx^d)$
4-parameter model[iv]	4	$y = a\ [c-(c-1)\exp(-bx^d)]$
Hill family		
3-parameter model[iii]	3	$y = a\ [1-x^d/(b^d + x^d)]$
4-parameter model[iv]	4	$y = a\ [1 + (c-1)x^d/(b^d + x^d)]$

Existing guidance
designed for controlled animal experiments

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- The analysis of human dose–response data can be more complicated than that of typical data from animal studies, due to confounders and imprecision in the exposure estimates.

- **In principle, the BMD approach would also be applicable to human data.**

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- In principle, the BMD approach would also be applicable to human data.

Benchmark Dose Technical Guidance

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

- Opportunities for modelling human data are more limited. Studies are less standardized and the modeling often involves additional considerations, such as adjusting for covariates.
- **Sometimes human toxicological data are reported in ways that are similar to animal data .... in these cases, this guidance document would be applicable**

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No further guidance on human studies is then given

Access to data

- Previously there have been few reasons to report data in a BMD usable format.
- **Humans ≠ animals:** Data protection rules apply
- Public health authorities need to do their homework as well to facilitate transfer of data

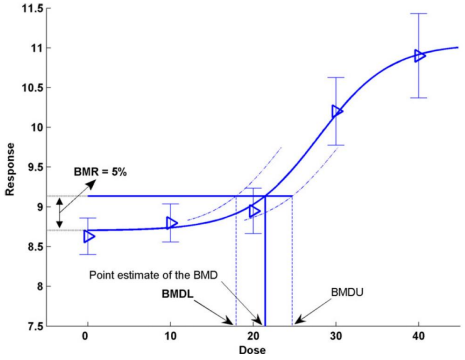
The NEW ENGLAND JOURNAL of MEDICINE
Perspective

"Transparency" as Mask? The EPA's Proposed Rule on Scientific Data

Joel Schwartz, Ph.D.

"The EPA recently proposed excluding from consideration in setting environmental standards any studies whose raw, individual-level data are not publicly available"

What characterises use of BMD modelling



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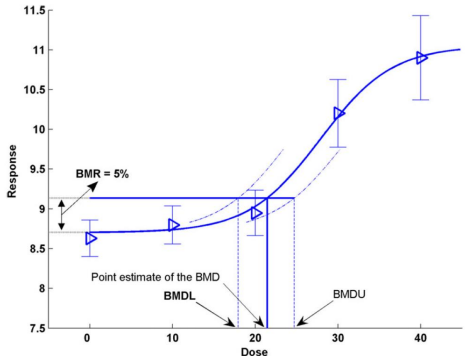


…for animal studies

In **animal** studies you have

1. **Controls (zero dose)**

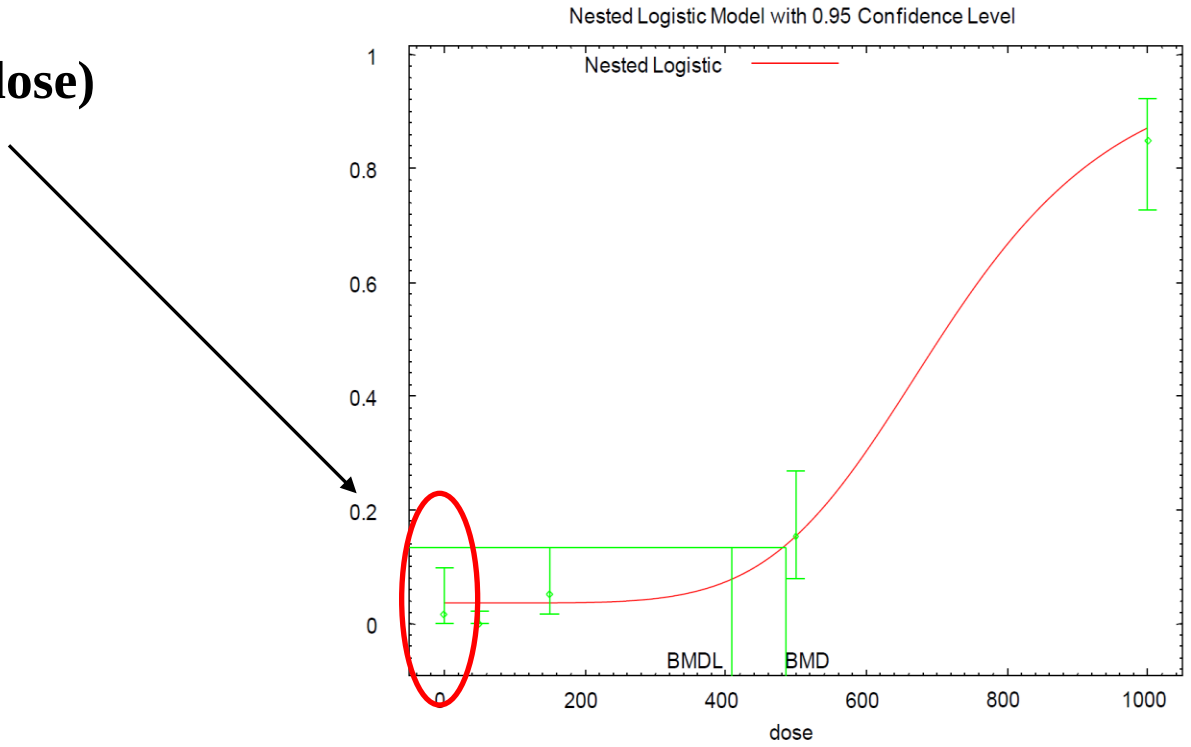


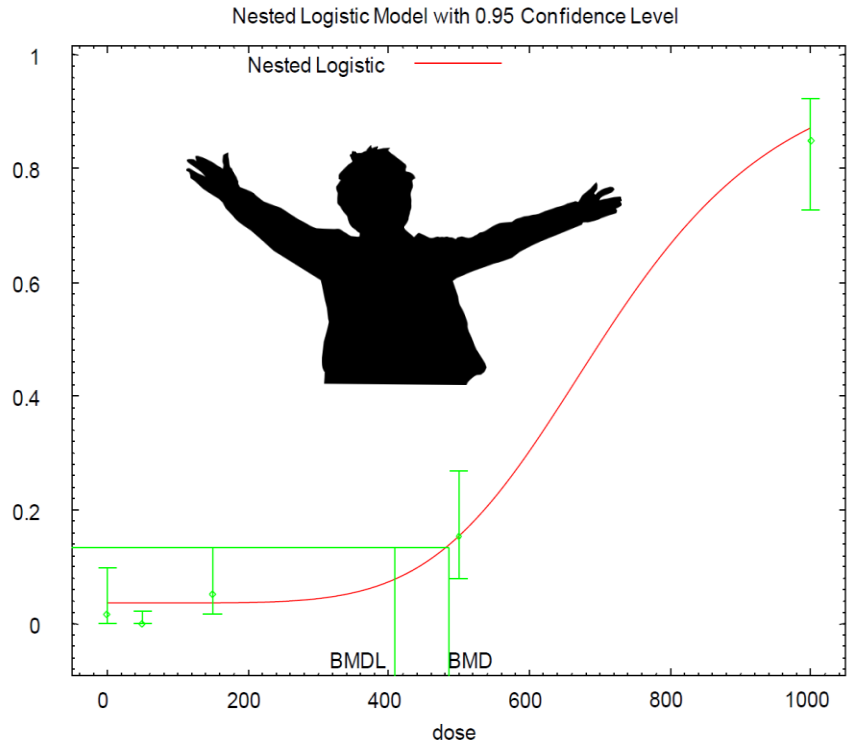
Figure A.5.1. Fraction of pups with skeletal malformations, and fitted nested logistic model.

George, JD et al 1992: The developmental toxicity of ethylene glycol diethyl ether in mice

In **animal** studies you have

1. Controls (zero dose)

2. **Large exposure range**
   1000-fold here



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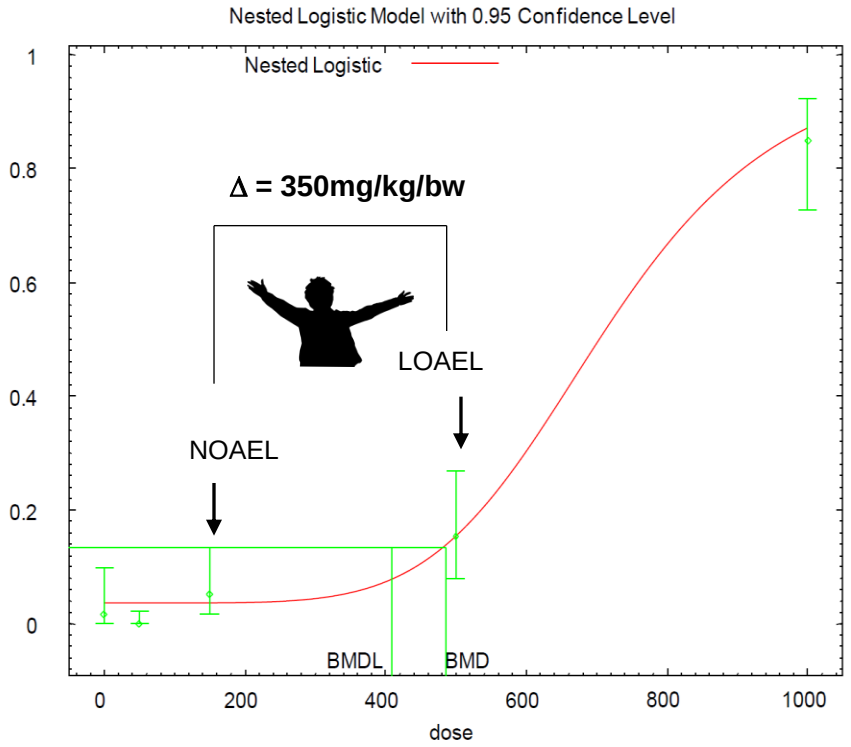
In **animal** studies you have

1. Controls (zero dose)
2. Large exposure range
3. **Large spacing between doses** (not always)



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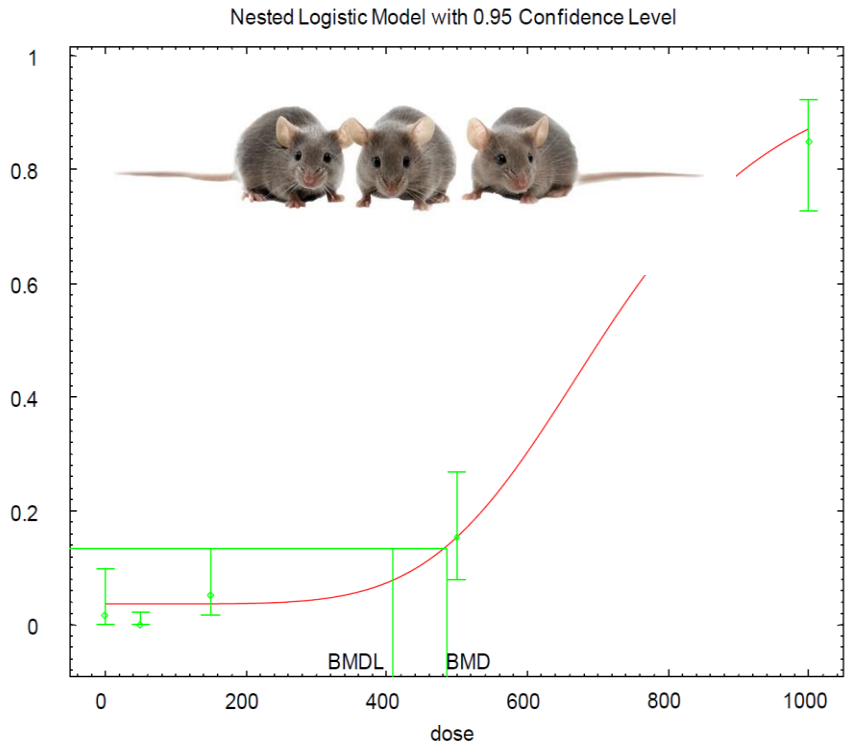
In **animal** studies you have

1. Controls (zero dose)
2. Large exposure range
3. Large spacing between doses
4. **Variability is small**



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In **animal** studies you have

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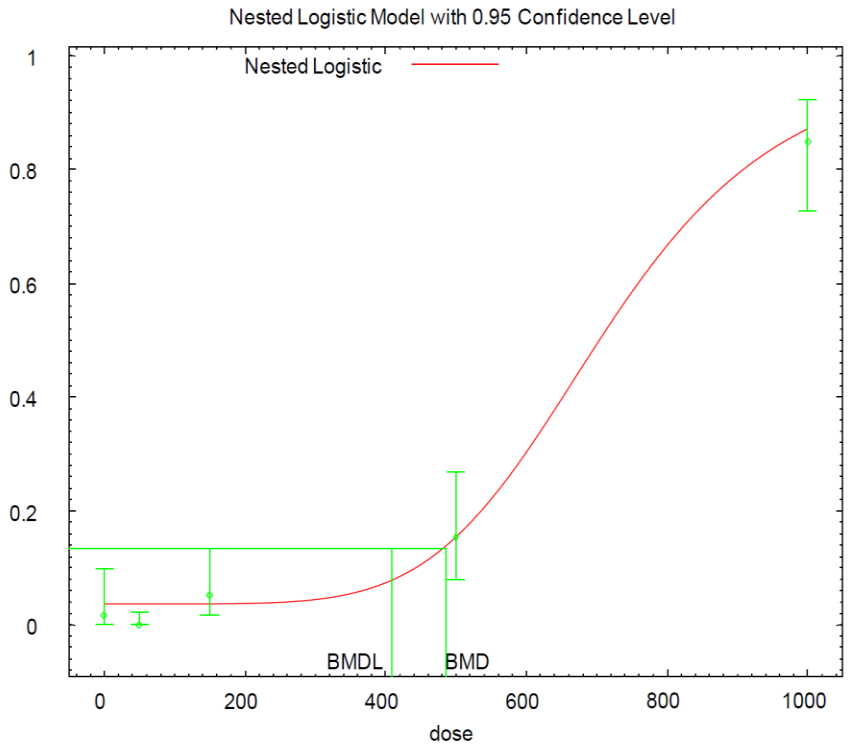
2. Large exposure range
3. Large spacing between doses
4. Variability is small
5. **<u>Controlled conditions</u>**



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… and after that: **uncertainty factors**

HSE

Supporting Publications 2013:EN-413

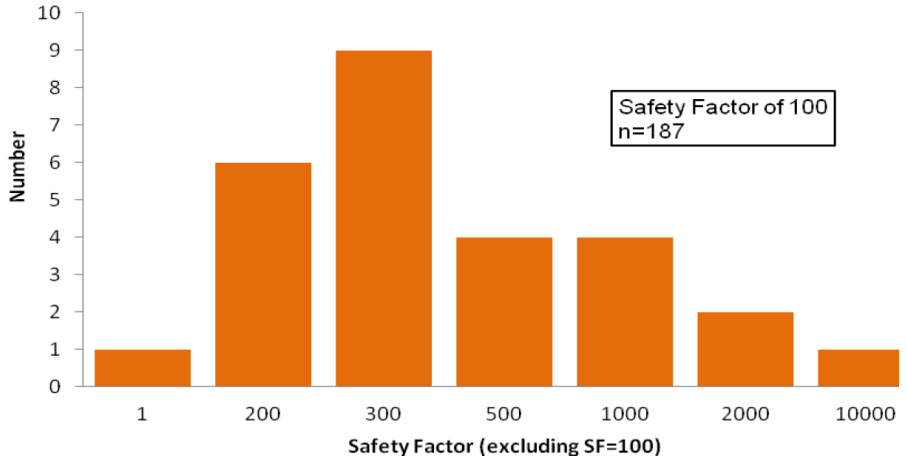
EXTERNAL SCIENTIFIC REPORT

Investigation of the state of the art on identification of appropriate reference points for the derivation of health-based guidance values (ADI, AOEL and AAOEL) for pesticides and on the derivation of uncertainty factors to be used in human risk assessment[1]

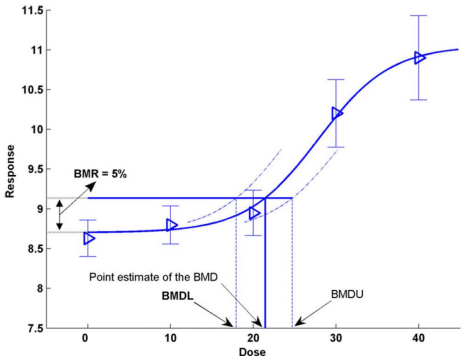
Chemicals Regulation Directorate, Health & Safety Executive, UK

N= 26

Range 1 – 10,000



What characterises use of BMD modelling



…for human studies

In **human** studies you have

1. **<u>No zero dose:</u>** just subjects with relatively low exposure

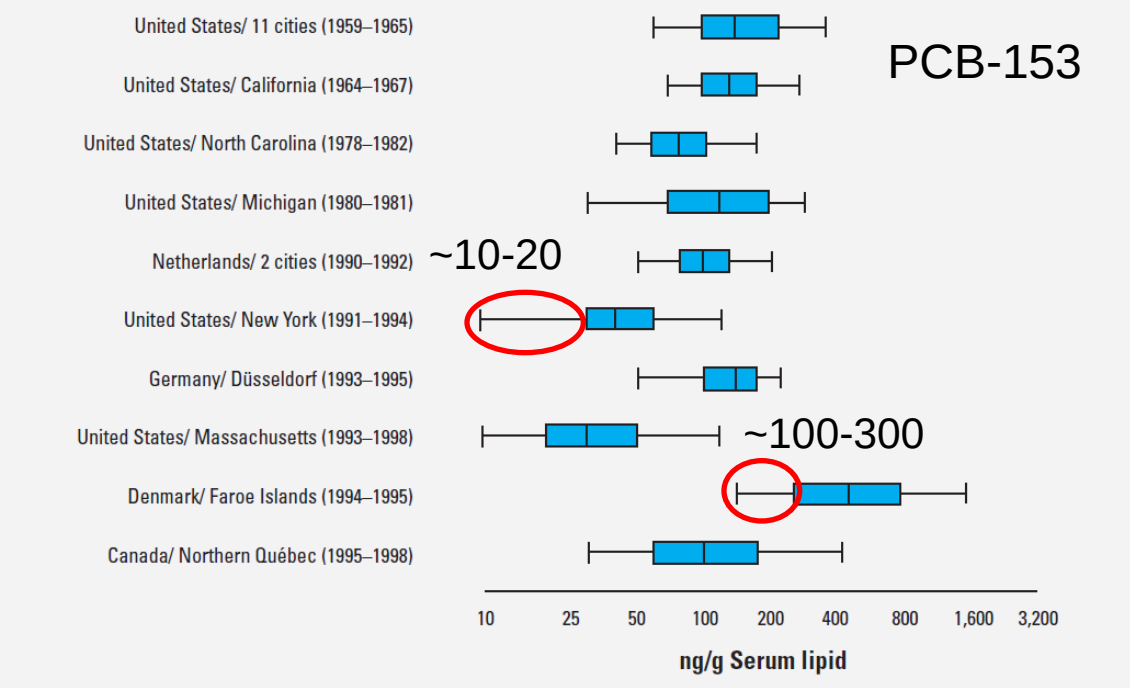
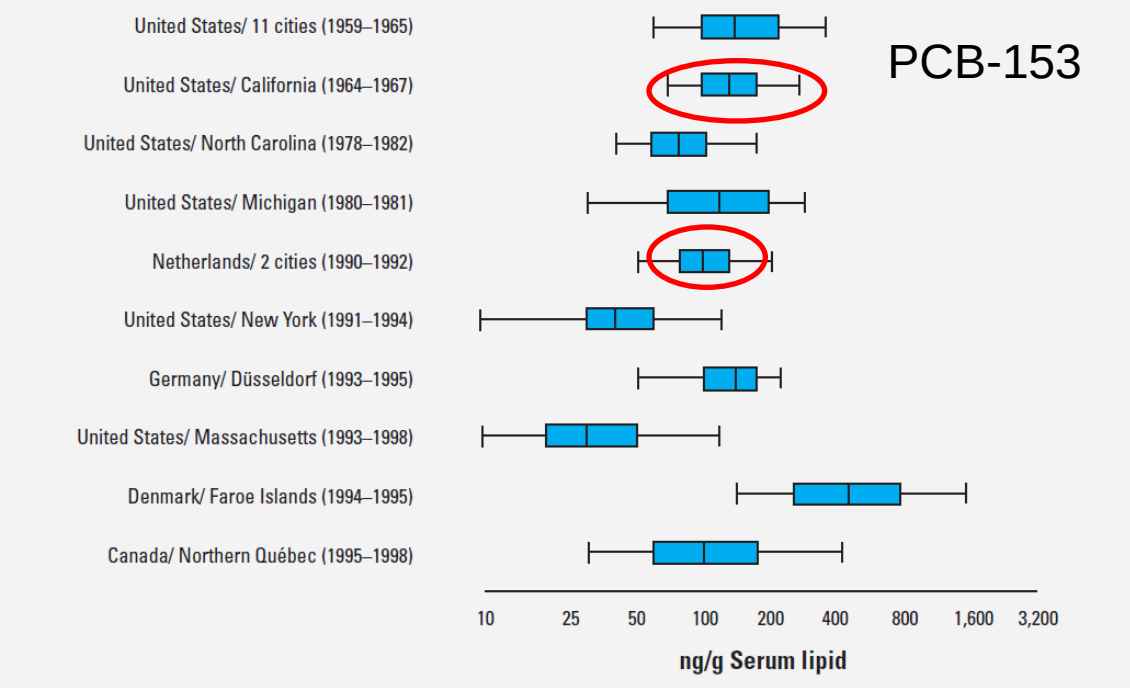


Figure 1. Percentiles of the distribution of PCB 153 concentration in serum (5th, 25th, 50th, 75th, and 95th), obtained using methods to express levels in a uniform manner. Data from 10 studies of neurodevelopment in humans.

In **human** studies you have

1. No zero dose: just subjects with relatively low exposure

2. **Often narrow exposure range**



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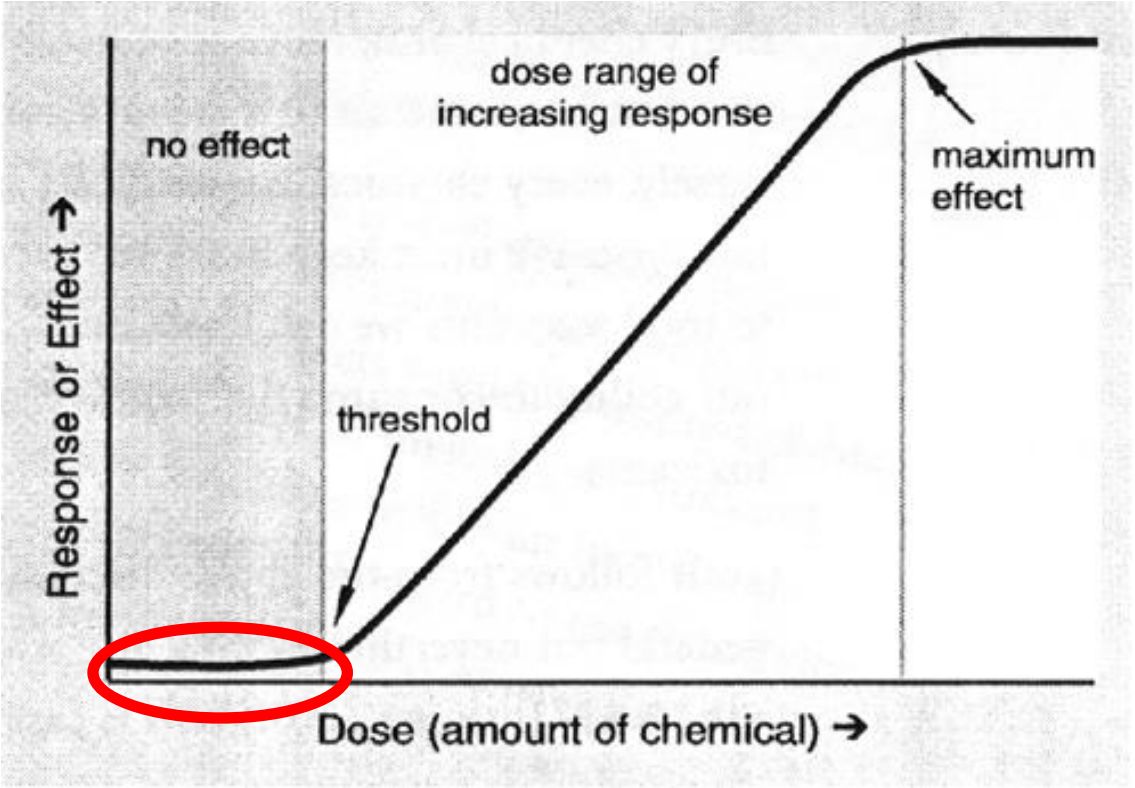
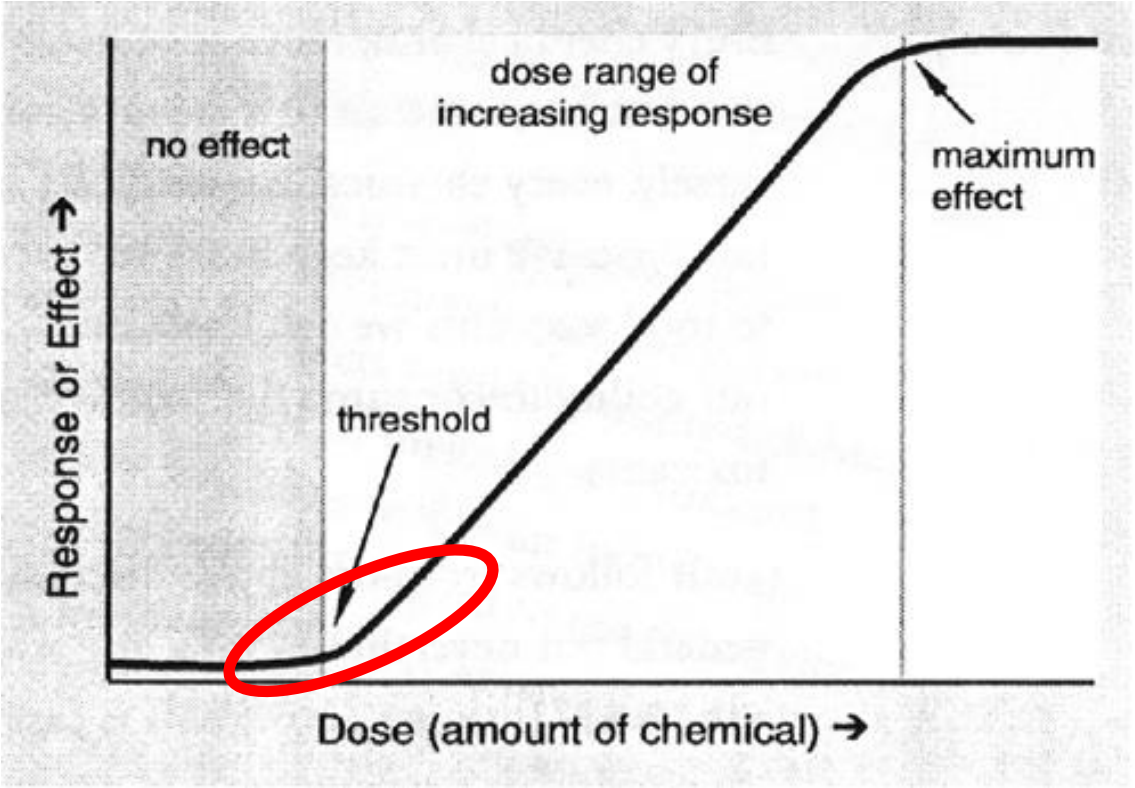
In **human** studies you have

- And this determines where your observations are placed on the theoretical dose-response curve:
  - **NULL**



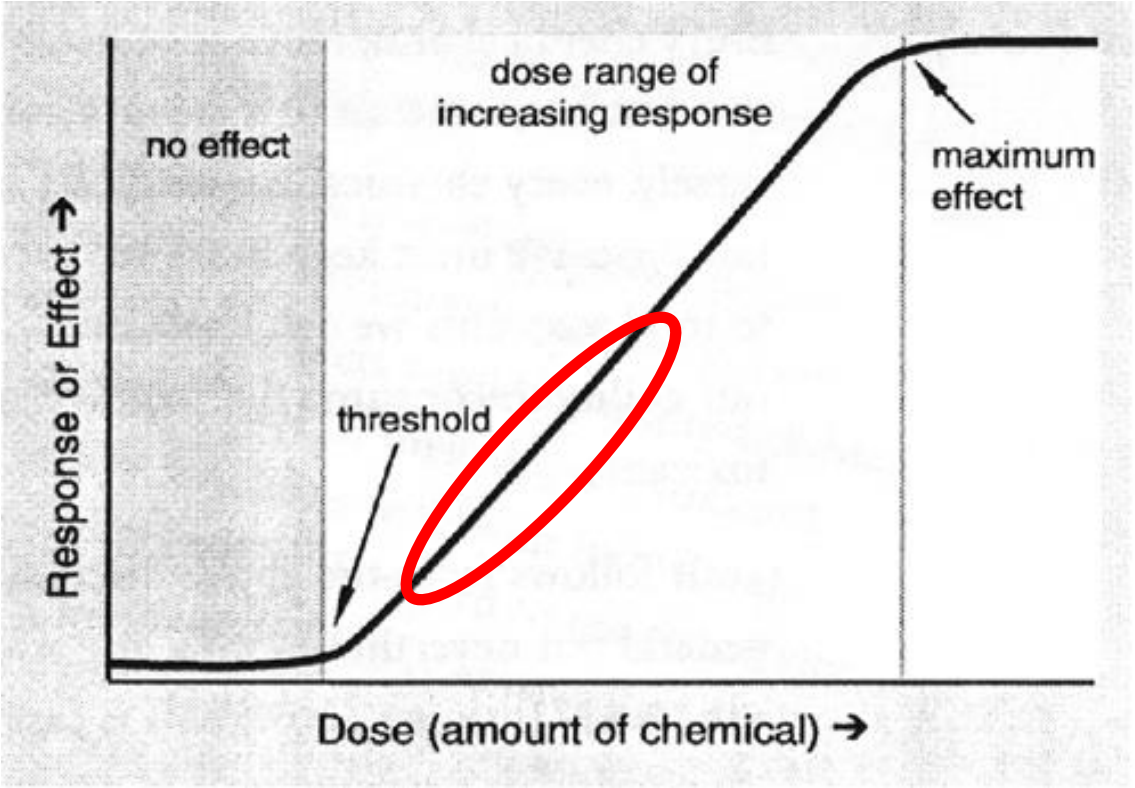
In **human** studies you have

- And this determines where your observations are placed on the theoretical dose-response curve:
  - NULL
  - **Non-Linear**



In **human** studies you have

- And this determines where your observations are placed on the theoretical dose-response curve:
  - NULL
  - Non-Linear
  - **or ~linear response**



In **human** studies you have

3. **Spacing between doses is not a problem:** exposure is determined by how free living subjects behave individually

The NOAEL/LOAEL issue is often not relevant

The benefit of using BMD approach relates to estimating POD taking biological relevance into consideration

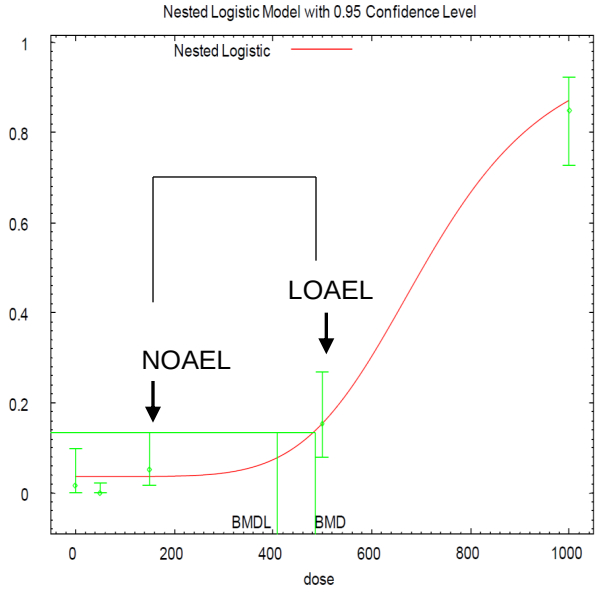


Figure A.5.1. Fraction of pups with skeletal malformations, and fitted nested logistic model.

In **human** studies you have

4. **LARGE variability** (it should be ☺)

   Raises some questions on the use of BMDLs

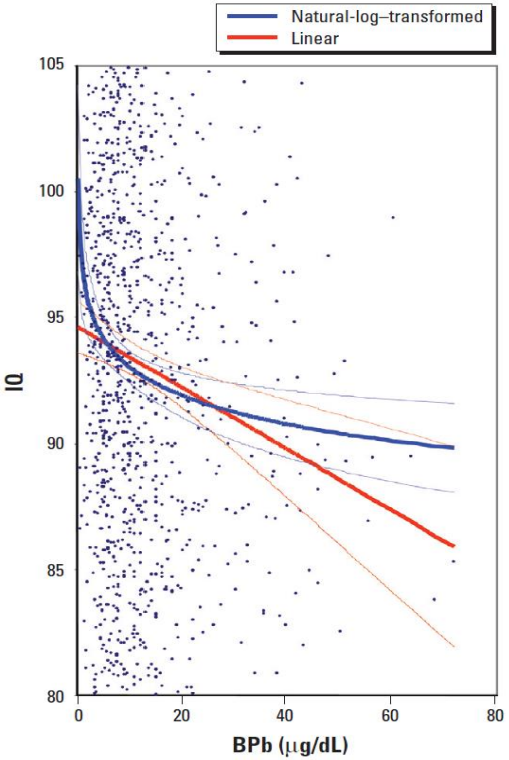


Figure 1. Partial regression plot of adjusted IQ (adjusted for natural-log lead model) and BPb (from Lanphear et al. 2005). The two regression lines (bold) with 95% CIs (narrow lines) represent the best-fit estimates of the relationship between IQ and BPb for natural-log–transformed BPb and lin-

In **human** studies you have

1. No zero dose: just subjects with relatively low exposure

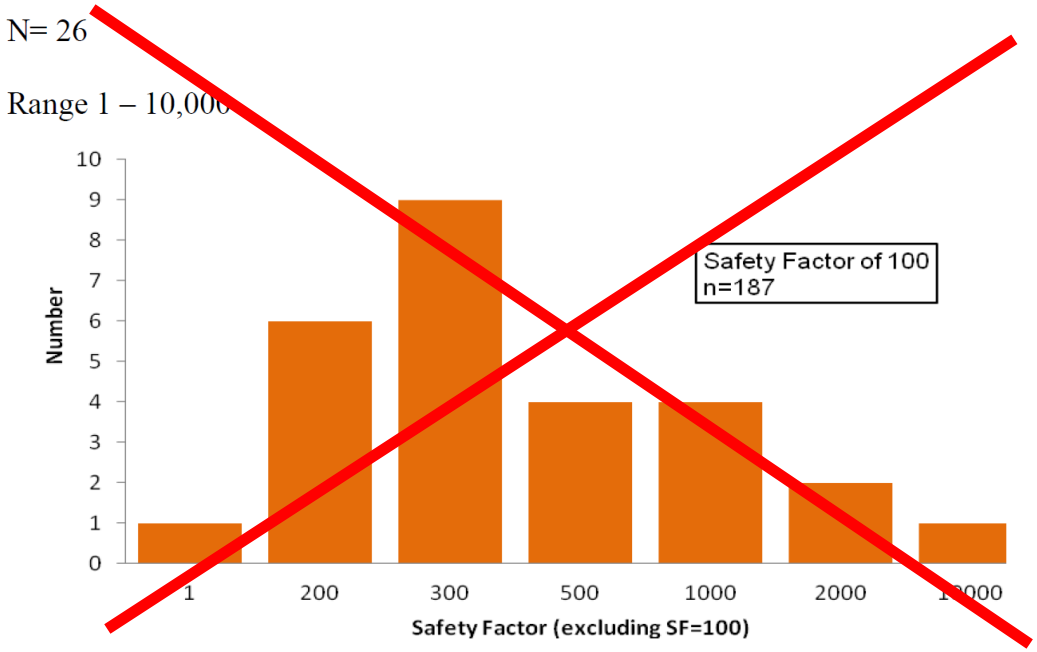
2. Often narrow exposure range

3. Spacing between doses are not a problem

4. Variability is LARGE

5. **And you cannot have controlled conditions**

Usually no uncertainty factors



- What you see is what you get -

Conclusion

- There are no major obstacles for using human data to derive HBGV
- BMD analyses can easily be performed but existing conventions may not be directly applicable and more work is needed (as has been done for animal data)
- Lack of individual participant data is unlikely to be a key issue
- Due to high variability and varying sample size the use of BMDLs for human data needs some careful considerations
- Modelling should not be done for the sake of modelling.

Thank you

"Transparency" as Mask? The EPA's Proposed Rule on Scientific Data

Joel Schwartz, Ph.D.