Low Dose Effects – Impact on Risk Assessment

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Key questions for risk assessment (many more questions than answers!)

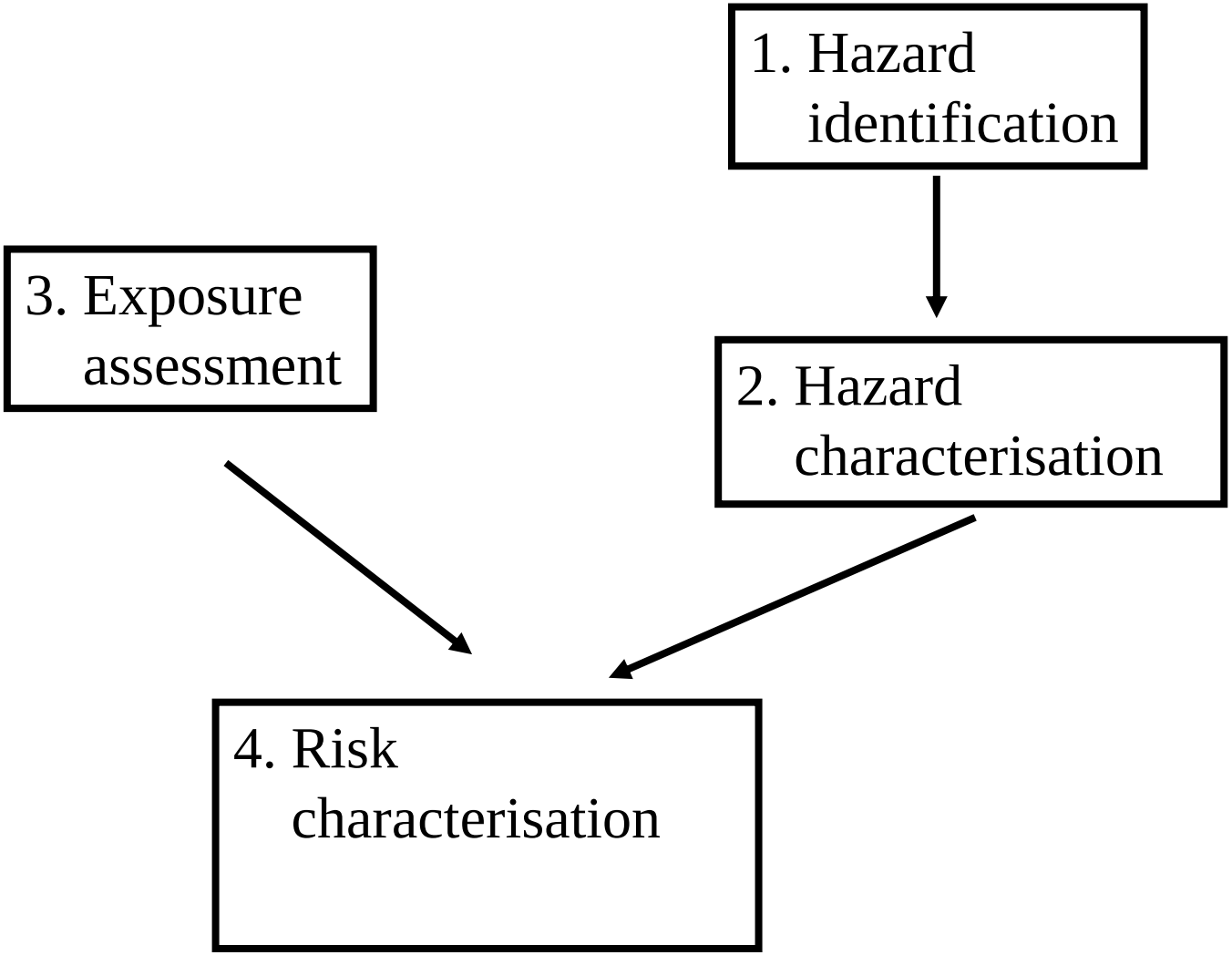
- are low-dose effects adverse (hazardous)?
- is the effect seen at the lowest dose the most relevant?
- is the effect reversible?
- is it within the normal homeostatic range for the parameter in question?
- what data do we need before we can use low dose effects in risk assessment?

Low Dose Effects – Impact on Risk Assessment

- **Low dose effects may indicate a hazard, but are they relevant for risk assessment?**

$64,000,000

Risk Assessment



Hazard versus risk (IPCS, 2004)

- **Hazard: Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub) population is exposed to that agent.**

- **Risk: The probability of an adverse effect in an organism, system or (sub)population caused under specified circumstances by exposure to an agent.**

Hazard characterisation

(dose-response, thresholded effects)

- **NOAEL: Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organism under defined conditions of exposure (WHO, 2009)**

- **NOAEL:The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects (US EPA)**

  - **Point of Departure for derivation of a health-based guidance value e.g. ADI/TDI**
  - **Calculation of a MOS**

Hazard characterisation

(non-thresholded and thresholded effects)

- **Benchmark dose (BMD):dose level, derived from the estimated dose-response curve, associated with a specified change in response, the Benchmark Response (BMR)**

- **BMDL:lower one-sided confidence limit of the BMD**
  - **POD for the derivation of a health-based guidance value**
  - **calculation of an MOE**
  - **starting point for linear low-dose extrapolation**

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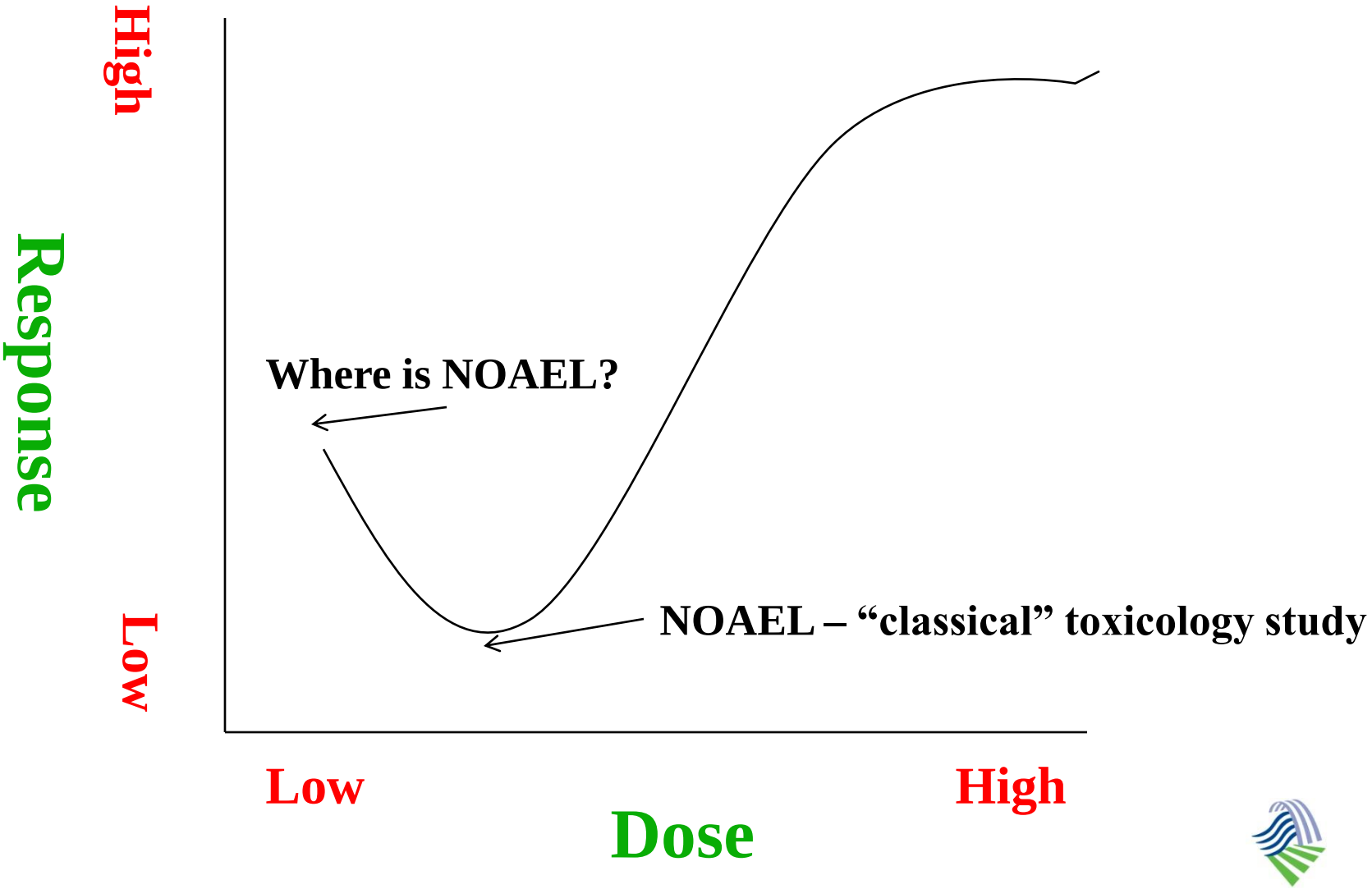


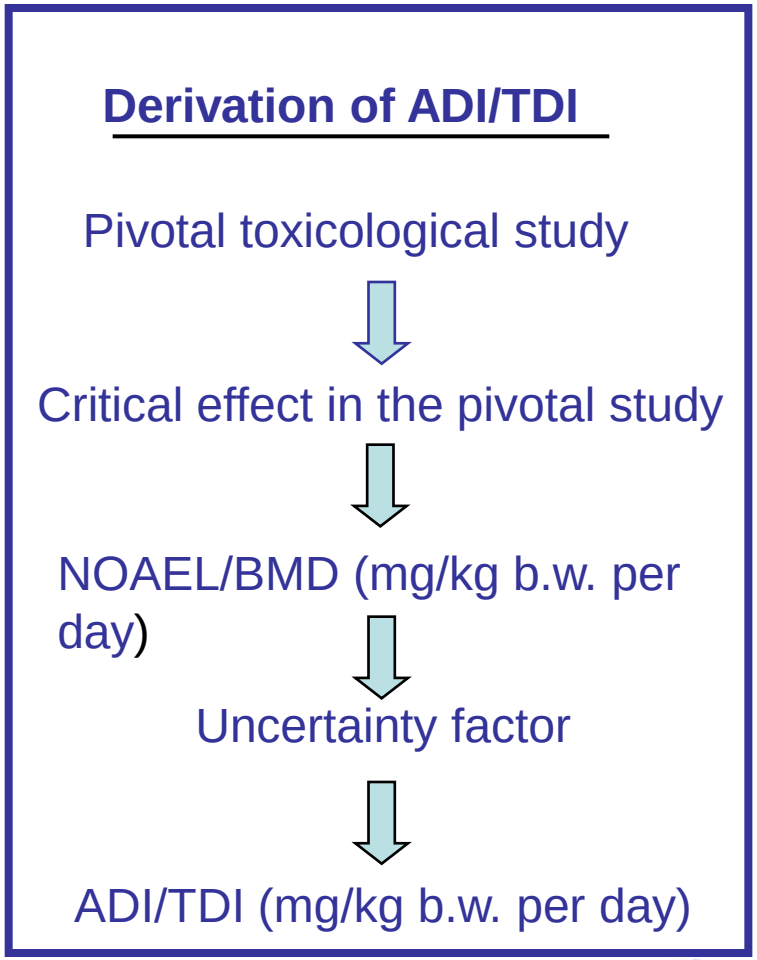
Hazard characterisation

Derivation of ADI/TDI

- **ADI/TDI: an estimate of the amount of a substance, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk**

- **established to protect the most sensitive subpopulation, based on the most sensitive critical health outcome**

- **use of uncertainty factors are considered to take into account differences in sensitivities in human populations, particularly from genotypic and phenotypic variations.**

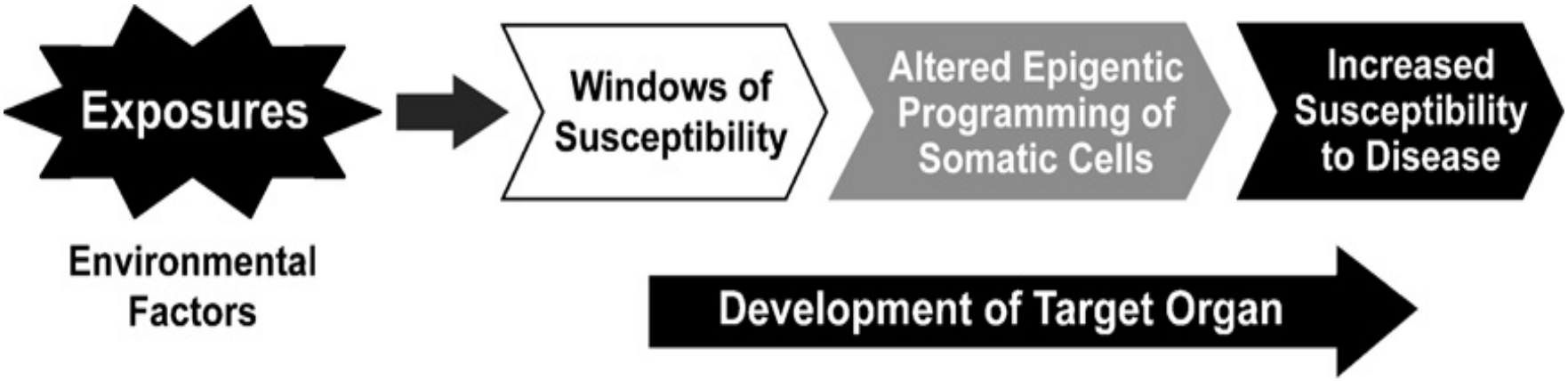


Data for derivation of NOAEL/BMD

- **NOAEL/BMD is identified from the most sensitive study in the most sensitive species**
- **Risk assessors have traditionally identified NOAELs/BMDs from animal studies forming part of the "standard" toxicological testing strategy**
- **Are these adequate to detect low-dose effects?**
- **How to take results of mechanistically-based studies lying outside the "standard" toxicological testing strategy into account in risk assessment?**

Windows of susceptibility

Exposure during a critical period of development may result in enhanced toxicity and/or toxicity expressed later in life



From: Schug et al. / Journal of Steroid Biochemistry & Molecular Biology 127 (2011) 204– 215

More key questions for risk assessment

- **Who are we trying to protect?**
- **Is an ADI/TDI sufficiently protective to protect the most sensitive subpopulation. One model for all?**
- **Do current testing paradigms sufficiently take into account windows of susceptibility?**

Additional uncertainty factors for infants and children – current practice

- **The ADI/TDI is considered to cover all sensitive segments of the human population, irrespective of age.**

- **If infants and children are most sensitive to a particular compound, that evidence must drive the derivation of the ADI/TDI.**

- **Therefore, no additional uncertainty factor and consequently no separate ADI/TDI should be established for infants and children.**

Other issues

- **Route of exposure used in the most critical studies?**
- **Weight of evidence approach?**
- **How would we use hazard versus risk as a basis for regulation?**

Low Dose Effects – Impact on Risk Assessment

- **Assuming a general acceptance of the scientific validity of the low dose/non-monotonic dose response curve hypothesis .....**
- **this could/does dictate a need for new risk assessment approaches**
- **do we abandon the classical risk assessment paradigm?**

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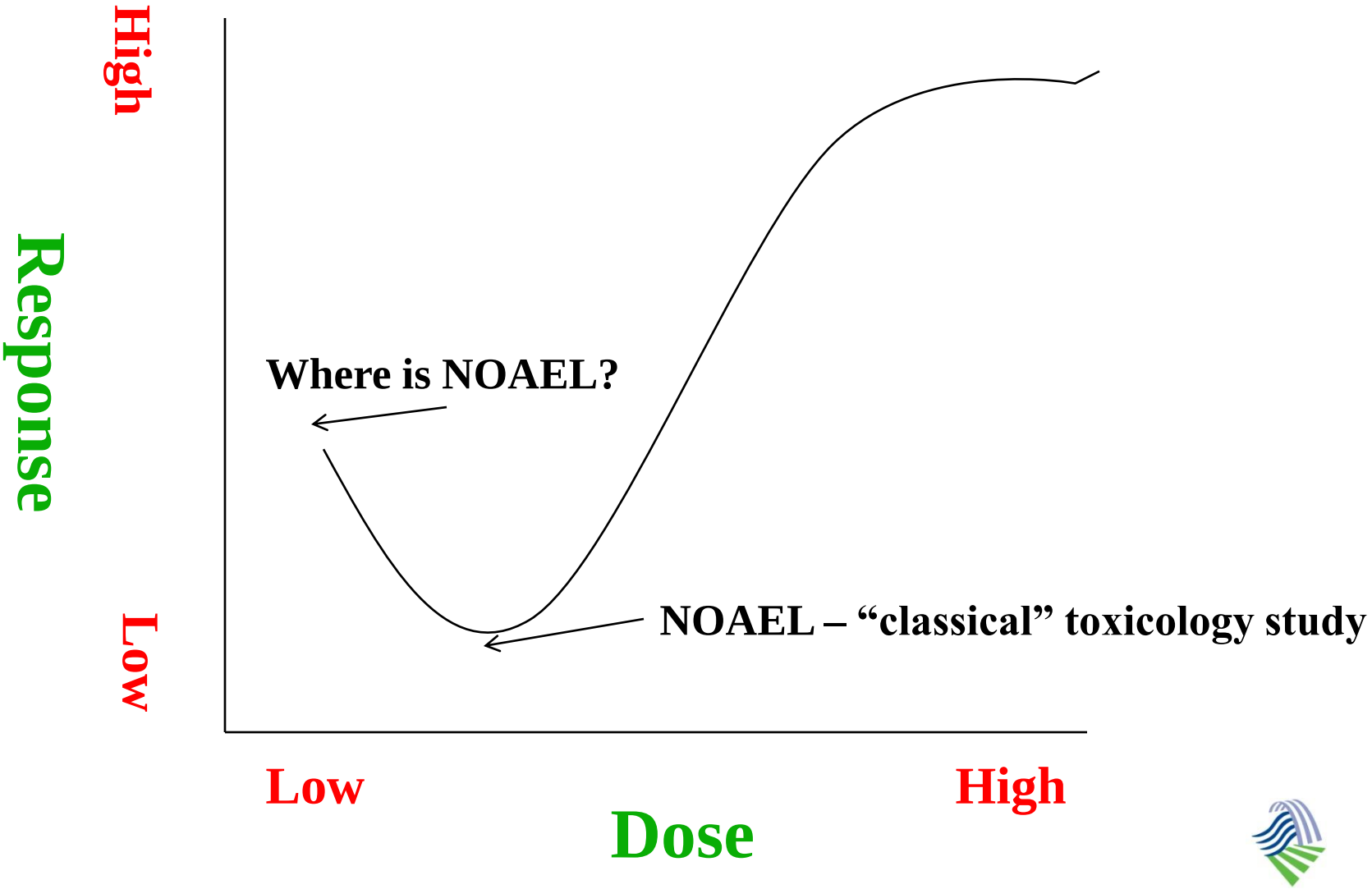

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- **Can different approaches already in use in risk assessment be used when dealing with low-dose effects and non-monotonic dose-response curves, e.g.**
  - **additional uncertainty factors**
  - **Margins of Exposure**
  - **Low dose extrapolation**
  - **Others?**

- **what data gaps need to be filled ?**

What data gaps need to be filled ?

- **Proof of adversity (human epidemiology?)**
- **Temporal association (human epidemiology, tissue level concentrations)**
- **Further toxicokinetic data linked to critical windows of exposure**
- **Definitive toxicological studies (e.g. NTP?)**
- **Mechanistic plausibility/mode of action**
  - **Already sufficient?**

Many argue that these data already exist

Conclusions

- **Consideration of the impact of low dose responses on the risk assessment process will require**
  - **rigorous evaluation of the shape of the dose response curve**
  - **scientifically-based decisions regarding the adverse nature of effects seen at low doses**
  - **consideration of study designs incorporating endpoints beyond current OECD methods**
  - **new risk assessment approaches?**