Low Dose Effects – Impact on Risk Assessment

Dr Iona Pratt
Food Safety Authority of Ireland
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

1. Hazard identification

2. Hazard characterisation

3. Exposure assessment

4. Risk characterisation
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 effects 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
Low Dose Effects – Impact on Risk Assessment

Where is NOAEL?

NOAEL – “classical” toxicology study
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.

Derivation of ADI/TDI

1. Pivotal toxicological study
2. Critical effect in the pivotal study
3. NOAEL/BMD (mg/kg b.w. per day)
4. Uncertainty factor
5. ADI/TDI (mg/kg b.w. per day)
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

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?
Low Dose Effects – Impact on Risk Assessment

NOAEL – “classical” toxicology study

Where is NOAEL?
Low Dose Effects – Impact on Risk Assessment

- 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?