Acute Inhalation Toxicity testing; The 3Rs, Current needs and Future Prospects
CRD is part of the HSE – HQ Bootle Merseyside

- REACH (CA)
- EU BPR (CA)
- PPPR (CA)
- CLP (CA)
- OEL and other COSHH-related activities
- Prior Informed Consent (PIC) DNA
HSE Bootle
Acute Inhalation Toxicity testing; The 3Rs, Current needs and Future Prospects

• What the current regulatory needs are
• Scope for use of the 3Rs
  - Reduction
  - Refinement
  - Replacement
• Future prospects for acute inhalation toxicity testing
EU Regulatory Schemes

- Industrial Chemicals - REACH
- Biocidal Products
- Plant Protection Products
- All are EU Regulations
Aims of REACH

• To ensure a high level of protection of human health and the environment from chemical hazards (Article 1);

• To ensure the free circulation of substances on the internal market while enhancing competitiveness and innovation (Article 1);

• To promote the development of alternative methods for the assessment of hazardous substances (Article 1)
• REACH Standard Information Requirements
• Tiered dependent on tonnage
• Annex VII 1-10 tpa – no requirement for inhalation information
• Annex VIII 10-100 tpa: Column 2; 8.5.2
• Second acute study, dermal or inhalation

“Testing by the inhalation route is appropriate if exposure of humans is likely taking into account the vapour pressure and/or the possibility of exposure to aerosols, particles or droplets of inhalable size”
• Testing Proposal is not required (cf Annexes IX and X)
For REACH, new animal testing should be undertaken only as a last resort (Art 13)

Specific exposure waiver Annex VIII, 8.5.2

General adaptations from standard information requirements (REACH Annex XI)

- Use of existing data (equivalency)
- Weight of Evidence
- QSAR/SAR (must use QMRF/QPRF)
- In vitro approaches (Annex XI, 1.4)
- Grouping and Read across
- Testing is not technically possible
Biocides and Plant Protection Products – Active Substance Data Requirements

- Tonnage independent of REACH
- Requirement that the 3Rs are taken into account before new testing (similar to REACH)
- Acute Inhalation Study, Required on Active Substance
  - The active substance has a vapour pressure > $1 \times 10^{-2}$ Pa at 20°C;
  - The active substance is a powder containing a significant proportion of particles of a diameter < 50 µm (> 1% on weight basis);
  - The active substance is included in products that are powders or are applied by spraying.
- We sometimes see acute inhalation studies conducted on milled materials for non EU schemes
Plant Protection Products – Data Requirements

- If the plant protection product or of the smoke it generates.

(a) is a gas or liquefied gas;
(b) is a smoke generating plant protection product or fumigant;
(c) is used with fogging/misting equipment;
(d) is a vapour releasing plant protection product;
(e) is supplied in an aerosol dispenser;
(f) is in a form of a powder or granules containing a significant proportion of particles of diameter < 50 μm (> 1 % on a weight basis);
(g) is to be applied from aircraft in cases where inhalation exposure is relevant;
(h) contains an active substance with a vapour pressure > $1 \times 10^{-2}$ Pa and is to be used in enclosed spaces such as warehouses or glasshouses;
What do we do with the data

- Classification and Labelling (CLP Regulation or UN GHS)
  - Acute Toxicity
  - identification of target organs (STOT SE)
  - Respiratory tract irritation
- Risk Characterisation
- Approval of products (Biocides and Pesticides)
- Land Use Planning
- Classification for acute toxicity and land use planning historically based on a point estimate of the LC50
Application of the 3Rs

• Reduction, Refinement or Replacement?
• OECD TG 403 can use up to 40 animals (5/sex/concentration) and uses lethality as the end point

• Reduction in animal numbers
• OECD TG 436; fewer animals but retains death as the end point

• Reduction and Refinement
• Draft OECD TG 433 (FCP), comparable to TG 436, but uses evident toxicity as the end point – a predictor of severe effects
• Both 433 and 436 use a series of defined “fixed concentrations”
The fixed concentration procedure (FCP) (draft OECD TG 433) uses fewer animals and ‘evident toxicity’ instead of death as an endpoint.

Is the inhalation equivalent of the Fixed Dose Procedure (TG 420).

‘Evident toxicity’ is defined as “clear signs that predict exposure to a higher concentration will cause severe toxicity or death in most animals.”

Use of evident toxicity means testing at a higher potentially toxic concentration can then be avoided.
What about the last R - Replacement

- It is likely there will be a need for acute inhalation information for the foreseeable future.
- There are no replacements to the standard animal models on the horizon.
- The best approaches may well be the “organ on a chip”.
- What replacements have to do is give information which can be used for regulatory purposes.
- This is not necessarily the same as giving LC50 values.
Impediments to further reductions in animal use – acute inhalation toxicity testing

• Biggest hurdle is acceptance of refined OECD TGs (in particular draft TG 433) across regulatory jurisdictions
• The challenge of evident toxicity
• New regulatory approaches which don’t require a point estimate of an LC50
• The OECD Mutual Acceptance of Data provisions should be respected, as far as possible
• May also need some revisions to national information requirements - non OECD countries
• These changes can only be achieved through dialogue
Questions ?