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Acute Inhalation Toxicity testing; The 3Rs, Current needs and Future Prospects

CRD

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

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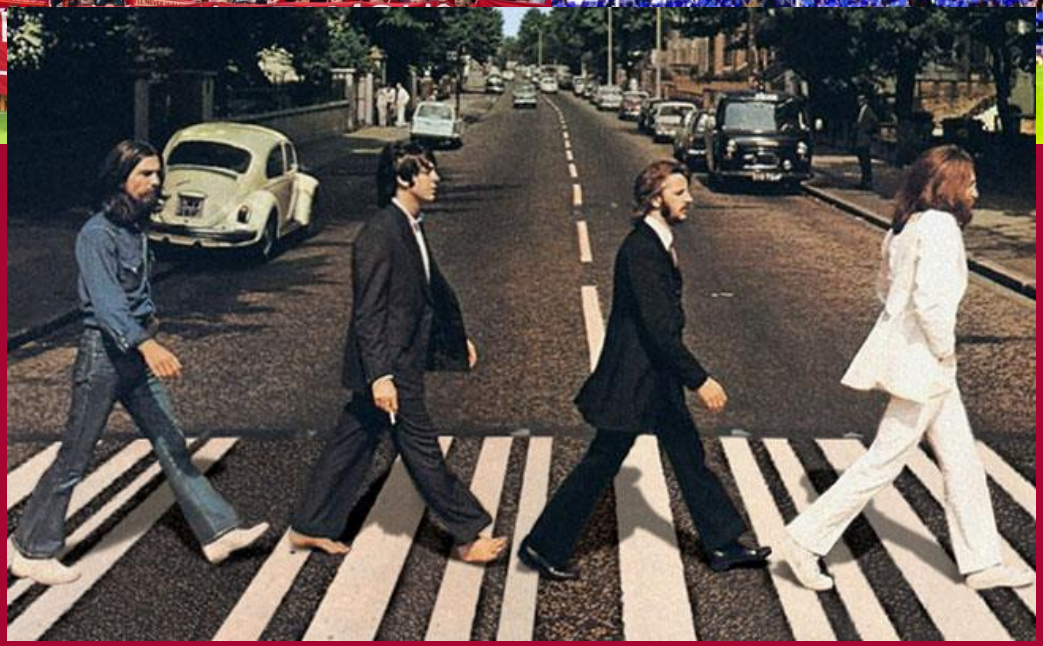

Acute Inhalation Toxicity testing; The 3Rs, Current needs and Future Prospects

- 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 Acute Inhalation Toxicity Information

- 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 areosols, particles or droplets of inhalable size"

- Testing Proposal is not required (cf Annexes IX and X)

REACH - Waivers

- 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 cf 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 × 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 × 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 Inhalation FCP, Draft OECD TG 433

- 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 ?