DNEL setting using ECHA Guidance: NMP and DCB as examples

REACH and Occupational Safety and Health (OSH) Legislation

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Quantitative measures of hazard used under REACH

- DNEL = Derived No-Effect Level for substances assumed to have a threshold exposure level
- DMEL = Derived Minimal Effect Level for substances assumed to have no threshold exposure level, e.g. geno-toxic carcinogens
- To avoid the appearance of setting a safe level for a non threshold substance, DMEL's can be replaced by dose-response curves, e.g. in Authorisations and expressed as a level of risk, without pronouncing on acceptability; minimisation of exposure expected

Basic steps

1. Selection of applicable DNELs – many are possible (short term, long term, local, systemic, for exposure via oral, dermal or inhalation routes)
2. Selection of points of departure from ALL available applicable toxicological data; depends on:
   - Differing regulatory requirements/concerns
   - Information requirements for the applicable tonnage;
   - Information in the public domain;
   - Information required due to specific concerns.
3. Scaling; from experiment to real-life; assumed to influence effects in a linear way; dose descriptor.
4. Dealing with other differences between experiment and real life and sources of uncertainty:
   Assessment factors

When are DNELs used in REACH?

- Registration
- Restriction
- Authorisation

Where there is a quantitative risk assessment

Which substances?

- Ones with an effect threshold

Which populations and exposures?

- In general: dermal and inhalation for worker; oral, dermal and inhalation for consumers and Man via the Environment
  - Authorisation applications contained both dermal and inhalation exposure data and assess those risks

Examples: varied scope of a restriction

- 1,4-dichlorobenzene – protection of workers (professionals) and consumers in general - no health effect specified
  - ECHA dossier at the request of the Commission

- N-methyl pyrrolidone – specific proposal to protect pregnant women in the workforce
  - Dossier Submitter: The Netherlands
  - Consumer use addressed in parallel under CLP by proposing removal of the specific concentration limits and applying the general limit of 0.3%

NMP - use

- Aprotic solvent - very specific molecular properties
- Broad spectrum of uses
  - Wire coating, solvent for pharmaceutical synthesis, pesticides, cleaning agent, etc
- Exposure in the workplace perceived as very variable

N-methyl pyrrolidone (NMP)

- Proposal specifically identifies risks to pregnant female workers
  - CLP classification – Repr. 1B ("presumed reprotoxicant" based on animal studies)
- Refers to the levels used in registration dossiers
- Considers several risk management options including a total ban but favoured exposure limits:

  NMP may only be manufactured and used if it can be guaranteed that under normal operating conditions the exposure (as 8-hr TWA) will remain below 5 mg/m^3, etc.
- Also proposes to limit dermal exposure

NMP Inhalation DNEL

- Starting point – NOAEC 247 mg/m^3 - Saillenfait et al. (2001, 2003)
- Dose descriptor correction for study design
  - Corrected for exposure duration: 6 hours animal exposure vs 8 hours working day, and for higher inhalation rate in humans during work (10 vs 6.7 m^3/day)
  - No correction factor was used for the duration of the study - developmental toxicity studies
- Interspecies differences: for remaining differences AF of 2.5
- Intraspecies differences – for workers: AF of 5,
  - for pregnant workers – use of an AF of 10 (for the general population) as proposed by the Dossier Submitter was rejected by RAC

Proposed inhalation DNEL: 10 mg/m^3

Dermal

NMP current status

- RAC adopted its opinion on NMP in June, SEAC agreed (pending final public consultation) its opinion on the socio-economics and effectiveness of the proposed restriction in September – nearing adoption
- DNEL (inh.) and IOEL differ by a factor of 4
- National OELs differ much more widely
- RAC recommended that the application of inhalation and dermal DNELs would form the most suitable risk management option
- The Commission is considering how to proceed with the restriction proposal on NMP

1,4 dichlorobenzene

- Dichlorobenzene, used as an air freshener in toilet blocks
  - The 'block' refers to the form of the solid air freshener and not to a building!
  - Public toilets with concierge and home bathrooms were considered and exposures modelled
- The substance has a Carc. 2 classification
- All available animal studies were considered, and DNELs calculated for all relevant endpoints
- RAC reviewed all the effect data and based their evaluation of the risk related to exposure to DCB on a DNEL for carcinogenic effect (threshold)

Methodology

- Starting point: NOAEC 75 ppm / 451 mg/m^3, JBRC, 1995/Aiso et al.2005, **used in EU RAR**
- Dose descriptor correction for study design:
  - The difference in exposure duration (6h animal vs 8h worker)
  - Inhalation rate (6.7m^3 at rest vs 10m^3 for work)
  - Study duration – no AF used for 2 y study
  - Absorption rate via inhalation (60% - mouse vs 100% human)
- Remaining differences (interspecies): AF 2.5 – metabolism, differences in species sensitivity
- Dose-responce relationship – dose spacing, slope and shape of the curve, extent and severity of effects: AF 3 (range:1-10)
- Quality of the data base: AF 1
- Intraspecies variations: AF 5 – workers

Resulting DNEL for carcinogenic effect – 3.62 mg/m^3

DCB Restriction - outcome

- RAC agreed with the Dossier Submitter that there was a risk to both professional and consumer users of DCB in toilet blocks by inhalation
- RAC and SEAC agreed that the proposed Risk Management Option (a ban) would be the most appropriate
- The Restriction has since passed into law
- The DNEL differs significantly from the IOEL
  - However, a recent IOEL update proposal brings them closer (x3)

Differences between DNELs and IOELs

Methodology

Point of departure

- SCOEL always reviews the whole database
- RAC also reviews the whole database (also done in the registration dossier), unless the proposal is more specific, e.g. NMP and the protection of pregnant female workers
- RAC considers exposure via skin, and develops DNELs, SCOEL uses skin notations for some substances

- Assessment factors
  - SCOEL uses assessment factors according to its methodology
  - RAC uses the detailed set of Assessment Factors set out in the ECHA Guidance
    - The number of opinions demands standardisation
    - Consistent use is essential, hence the step-by-step approach

REACH Guidance

- Preparation of REACH Guidance is a collaborative effort
- It is open for consultation to stakeholders and reflects the views of a wide range of scientists and regulatory experts (MS, Industry and ECHA Committee members)
- 'R8' published in 2008 – principles have not changed – some additions made in the meantime (v2.1, 2012)
- The Guidance ensures the consistency and transparency of the RAC and other ECHA opinions, leaving room for scientific interpretation

- http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

Finally…….

- RAC and SCOEL will continue to collaborate on preventing conflicting reference values
- Calls for developing improved methodology welcomed
- Key issues for reflection/convergence:
  - Regulatory background, e.g. CLP status is relevant
  - Point of departure and priority of endpoints
  - Inhalation and dermal exposure
  - Allometric scaling
  - Assessment factors and uncertainty

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