Uncertainty in the use of Non-Test Data Under REACH – Example(s)

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Point of Departure

- Chemical industry in EU and beyond is advancing the Global Product Strategy (GPS) under the ICCA umbrella.
- GPS covers a base set of information on chemicals in commerce.
- Committed to Reduce, Refine and Replace animal testing
- Under ICCA LRI sponsoring of research on
  - Computational tools
  - Quality assured databases
  - Intelligent testing strategies
Traditional Regulatory Toxicology (i)

- Risk Assessment (RA) estimates the risks for:
  - Short term and chronic effects.
  - Local and systemic effects.
  - Individuals with different sensitivities.
- Uses tiered sets of animal tests:
  - Identify the critical effects
  - Set a Point of Departure (POD)
  - Derive route-specific reference doses or cancer potency factors.
- Account for remaining uncertainties using assessment factors
Traditional Regulatory Toxicology (ii)

- Has served well and prevented adverse impacts to humans and the environment.
- Is time consuming, expensive, and requires large numbers of animals.
- Resulted in uneven decision making – the ‘uncertainty paradox’ (Schaafsma et al, 2009).
  - Detailed assessment for few substances
  - Open-ended findings (each new study brings new uncertainties).

The REACH approach ... (bold print)

- Address a large set of substances in short time
- Start assessment from a minimal dataset (‘base-set’).
- Only generate information required for the assessment (e.g. external exposure based waiving).
- Allow for alternative methods and non-testing options to generate hazard information.
- Resolve the ‘uncertainty paradox’

Small print
- Risk assessment approaches (reference dose) have been moved to the hazard assessment. – How to deal with uncertainty in the Hazard assessment?
Fig 1: Use of QSAR and Waiving for approx. 120 substances (2010 submission)
Non-testing approaches in practice

• Used for less complex endpoints where confidence in the result is high.
• By and large in a qualitative way to support choice of the (experimental) point of departure.
• QSAR is preferred for environmental endpoints; read across for mammalian endpoints.
• For complex endpoints, testing or waiving is preferred – reflects lack of confidence in non-testing approach.
• When the endpoint is not considered relevant (e.g. absence of chronic exposure), the known unknown is preferred to the uncertain ‘known’.
Uncertainty of non-testing under REACH

- Hazard assessment (feeding to Classification & Labelling)
- Hazard assessment (feeding to Risk Characterisation)
  - Uncertainty is inherent to hazard assessment.
  - The conclusion for the hazard assessment is based on weight of evidence with little room for ‘conservatism’.
  - Uncertainty should be accounted for in risk characterisation (e.g. AF).
- Test plan
  - Partially disconnected from risk characterisation.
  - Supporting ‘Scientifically’ unnecessary waiver.
## Uncertainty and approaches in RA

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>Guideline testing</th>
<th>Read across / QSAR for endpoint</th>
<th>QSAR on potential (cellular / in vitro)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Limited data</td>
<td>HH: AF 2 / 6</td>
<td>ERA: AF 5–100</td>
<td></td>
</tr>
<tr>
<td>2) Inter-Species Differences (False negative / positives)</td>
<td>HH: AF 2.5</td>
<td>ERA: AF 5–100</td>
<td>+ / – – + / – –</td>
</tr>
<tr>
<td>3) Intra-species Differences</td>
<td>HH: AF 10</td>
<td>ERA: –</td>
<td>+</td>
</tr>
<tr>
<td>4) ADME / System biology</td>
<td>HH: see 2)</td>
<td>ERA: –</td>
<td>++</td>
</tr>
<tr>
<td>5) Test material variability</td>
<td>+ +</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6) Test method</td>
<td>+</td>
<td>+ / --</td>
<td>–</td>
</tr>
</tbody>
</table>
Aquatic toxicity – Example 1

Starting point
- Large family with common functional group and variable alkyl chain length.
- Data gaps for selected species (Algae) for selected members.

Approach taken:
- Multiple QSARs applied to family.
- Choice of QSAR based on performance for known members of family – or own QSAR derived based on family data,
- Prediction used to conclude not most sensitive species.
- No Classification.
- Standard AF used for PNEC.
- Waiving based on low toxicity.

\[
\log E_{C50} = -1.1824 \times \log K_{ow} + 1.7717
\]

van Leeuwen et al, 1992
Aquatic toxicity – Example 2

Starting point
• Large family of hydrocarbons.
• Complex mixtures.
• Common mechanism of action (Narcosis)
• Common experimental challenges: Volatility, limited solubility.

Approach taken:
• Exp. data, QSAR (PetroTox), and read across for aq. endpoints.
• PetroTox selects representative molecules based on the composition of the test material and carbon block method.
• Estimates soluble fraction (WAF).
• Program Predicts LL50 and PNEC.
• PNEC were used as predicted.
• Classified Cat I Environment.
• No waiving (predicted /read across)
Human Health – Example 1

Starting point:
- Small 2010 family metabolites or analogue to metabolites of a product with full data package.
- Developmental tox. effects in (422) screening for metabolites and analogues.
- Similar effects (at lower rate) in full study.

Approach taken:
- Available 2-generation study (Rat), reproductive screening studies (rat) and developmental toxicity studies (rat and rabbit) used in read across for all substances.
- Read across is used to conclude on F2 effects.
- Classification and labeling: Based on Mode of action information.
- DNEL: driven by compound specific repeated dose – no change of AF.
- Test plan: No waiving (read across).
Human Health – Example 2

Starting point:
- Two families of ethoxylated or propoxylated or mixed products.
- Families based on reactive group of starting materials – alcohol (n=7) vs. amine (n=3).
- No or minimal and unspecific effects make mechanistic confirmation difficult.

Approach taken:
- Text book example ...
- Categories defined – selected members tested for repeated dose / repro screen.
- Read across NOAEL (no correction for MW etc.)
- No Classification required.
- No extra AF for DNEL.
- Waiving based on no effect incl. read across.
Account for uncertainty from non-testing (i)

- Guidance suggests additional safety factor to account for uncertainty.
- For larger datasets the ratio of experimental variability and predictivity of a validation dataset can be considered as measure for additional uncertainty (Predictivity of training data is susceptible to overparameterisation).
- Trends in toxicity within category can be concluded from other endpoints.
- For read across endpoints, the most toxic member is tested. Lower toxicity is not accounted for (obviously QSAR does).
Account for uncertainty from non-testing (ii)

- Vink et al. (2010) use assessment factor 2 for quantitative read across.
- Need for additional assessment factor is debatable. Relevant only if read across NOAEL is final point of departure or most sensitive EC50/NOEC.
- DNELs of lower tox products should be equal or higher not lower than the DNELs from the ‘donating’ molecule.
- To which extend should the assessment factors be lowered based on absence of e.g. structural alerts?

Conclusion

- Industry has used a cautious approach with the opportunity of non-testing information.
- Preference is given to read across for complex endpoints and out-of-the box-QSAR for less complex endpoints.
- The OECD principals request and support the assessment of uncertainty. Predictivity typically close to the experimental variability.
- If so, additional assessment factor seems unreasonable.
- The assessment factor does not account for false negatives.
Thank you for your attention