‘Integrated Testing Strategies’ for REACH

Perspective from the European Chemicals Agency

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Outline

- ECHA mission and role
- Registration and information requirements
- Need for ‘Intelligent’ (integrated) testing strategies
- Further necessary developments
Establishment of the European Chemicals Agency (ECHA) and its mission

Art. 75(1) and pre-amble 95 of REACH

- Manage all REACH related tasks by carrying out or coordinating the necessary activities, in order to ensure consistent implementation at Community level
- To provide the best possible scientific advice on questions related to the safety and socio-economic aspects of the use of chemicals
- by ensuring a credible decision-making process, using the best possible scientific, technical and regulatory capacities and
- by working independently in an efficient, transparent and consistent manner.
The Agency’s Structure

Management Board

Executive Director

Board of Appeal

The Committees
- Risk Assessment (RAC)
- Socio-economic Assessment (SEAC)
- Member State Committee (MSC)

The Forum

Secretariat

Member States Competent Authorities

Commission

Stakeholders

http://echa.europa.eu
REGISTRATION AND INFORMATION REQUIREMENTS
Substance to be registered

> 10 tonne/year

Substance dangerous or PBT/vPvB

Technical Dossier
- Identify of the manufacturer/importer
- Identity of substance
- Info-manufacture and use of the substance
- Classification and labelling
- Guidance on safe use of the substance
- Study summaries – substance properties
- Test proposals (if relevant)
- Exposure information

Chemical Safety Report
- Hazard and PBT Assessment

Chemical Safety Report
- Hazard and PBT Assessment
- Exposure Assessment
- Risk Characterisation AND
- Exposure Scenarios
## Information requirements

<table>
<thead>
<tr>
<th>Annex</th>
<th>Human Health</th>
<th>Environment</th>
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</thead>
<tbody>
<tr>
<td>Annex VII</td>
<td>• <em>In vitro</em> skin and eye irritation</td>
<td>• Short term toxicity (daphnia, algae)</td>
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<tr>
<td>(≥ 1 tpa)</td>
<td>• Skin sensitisation</td>
<td>• Degradation (biotic)</td>
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<td></td>
<td>• <em>In vitro</em> mutagenicity</td>
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<td></td>
<td>• Acute toxicity (one route)</td>
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<tr>
<td>Annex VIII</td>
<td>• <em>In vivo</em> skin and eye irritation</td>
<td>• Short term toxicity (fish)</td>
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<tr>
<td>(≥ 10 tpa)</td>
<td>• Further <em>in vitro</em> mutagenicity</td>
<td>• Respiration inhibition test</td>
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<td></td>
<td>• Acute toxicity (2nd route)</td>
<td>• Degradation (hydrolysis)</td>
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<td>• Short-term RdT (28 days)</td>
<td>• Fate (absorption/desorption)</td>
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<td>• Reproductive toxicity screening</td>
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<td></td>
<td>• Assessment of toxicokinetics (not a testing requirement)</td>
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<tr>
<td>Annex IX</td>
<td>• Further <em>in vivo</em> mutagenicity studies (if + results)</td>
<td>• Long-term toxicity (invertebrates, fish)</td>
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<tr>
<td>(≥ 100 tpa)</td>
<td>• Sub-chronic toxicity (90-days)</td>
<td>• Biotic degradation (simulation studies)</td>
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<td></td>
<td>• Reproductive toxicity tests</td>
<td>• Identification of degradation products</td>
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<td></td>
<td></td>
<td>• Fate: bioaccumulation in fish, further absorption/desorption</td>
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<td>• Short term toxicity- terrestrial organisms (invertebrates, MO, plants)</td>
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<tr>
<td>Annex X</td>
<td>• Further <em>in vivo</em> mutagenicity studies (if + results)</td>
<td>• Further biotic degradation</td>
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<tr>
<td>(≥ 1000 tpa)</td>
<td>• Further reproductive toxicity studies</td>
<td>• Further fate</td>
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<tr>
<td></td>
<td>• <em>Chronic toxicity (may)</em></td>
<td>• Long-term effects on terrestrial organisms</td>
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<tr>
<td></td>
<td>• <em>Carcinogenicity (may)</em></td>
<td>• Long-term or reproductive toxicity to birds</td>
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Increased use of animals and/or costs

“Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions of Annex XI are met.”
Annex XI: General rules for adaptation of the standard Testing regime

• Use of existing data (not GLP/ non standard tests)
• Historical Human data
• (Q)SAR
• Grouping of substances and read-across approach
• In vitro methods
• Weight of evidence
Meeting the information requirements 4 Steps:

1. Gather and share existing information
   - all relevant and available physicochemical, toxicological and ecotoxicological information;
   - assessment of reliability, relevance and adequacy for C&L, PBT/vPvB assessment, derivation of DNEL(s), PNEC(s);
   - information on use and exposure;
   - data sharing (Substance Information Exchange Forums - SIEFs).
Meeting the information requirements

2. Consider information needs (Annex VII-X)

- specific criteria in column 2 of Annexes VII-X for specific endpoints

- general criteria for adaptation in Annex XI:
  - scientific necessity (existing data, weight of evidence, (Q)SARs, in vitro, grouping/read-across);
  - technical possibility;
  - substance-tailored exposure-driven testing
Meeting the Information Requirements

3. **Identify information gap(s)**
   - comparison of information needs (step 2) with the available reliable and relevant information (step 1);
   - careful consideration of adaptation rules.

4. **Generate new data/Propose test**
   - data gap for information requirements in Annex VII, VIII; conduct a test before registration;
   - data gap for information requirements in Annex IX, X; submit a testing proposal to ECHA.

⇒ Animal testing undertaken as a last resort
Adaptation is not un-conditioned!

The conditions on the use of non-standard information in Annex XI refer in particular (but not only) to:

- adequacy and reliability of the coverage of the key parameters;
- scientific validity of the methods;
- adequacy and reliability of documentation
Use of information in a regulatory context

- Information needs to be adequate for Classification and Labelling and the Chemical Safety Assessment

- Industries’ responsibility to decide and justify which further information they consider necessary (starting from a minimum data set)
Adequacy of information?

e.g.:

- Provide, where possible, a quantitative estimate of the (no)effect level or probability that effect occurs
- Cover as much as possible the parameters investigated in the ’standard’ study
- If not, be clear on missing information (and potentially introduced additional uncertainty)
- Keep the ultimate goal of REACH into account:

→ safe use of chemicals ←
Key questions

• Are you prepared to install 5 million Euro exposure reduction installations on the basis on the basis of the outcome of a single positive in-vitro study?

• Are you prepared to accept widespread consumer exposure to a high production volume chemical for which the category approach shows it is not a reproductive toxicant?
Need for Integrated/Intelligent Testing Strategies!

• To get the “right information” to adequately identify and manage the risks
• To limit the number of animal tests
• To reduce the costs for industry
• To speed up the assessment process

• Extensive guidance developed with stakeholders involvement:

  “Guidance on information requirements & Chemical Safety Assessment”

http://echa.europa.eu
Elements of Integrated testing strategies

(Q)SARs

Read Across

In-vitro

Endpoint Information: Annexes VI-XI

Existing information

Waiving: • technical • exposure

TESTING

http://echa.europa.eu
Further developments

Guidance:

• “Guidance on information requirements and the CSA” is today’s baseline

• ‘Validation’ and improvement of the current ITSs through their application

• A “learning by doing process”

• Update of the guidance methodologies to reflect the regulatory experience obtained in the evaluation process as well as the new developments in science
Opportunities

for researchers/scientific community to explore and further develop methods/approaches, e.g.:

- **(Q)SARs:**
  - validity, transparency and availability of the existing models;
  - ‘long-term’ endpoints, toxicokinetics and metabolism.

- **Grouping approaches:**
  - specific groups of substances (mechanistic considerations);
  - quantitative read-across.

- **In vitro methods:**
  - not just replacement, but also screening, mechanistic insight.

- **Refinement/optimisation of in vivo methods**

- **Exposure considerations:**
  - generation of reliable exposure information;
  - Threshold of Toxicological Concern (TTC)
Further developments

- **Integration** of different methods/types of information

- Development of decision-supporting tools ((Q)SAR Toolbox)

- Training and familiarisation of all parties involved with new tools and strategies

- Increased accessibility to data and efficiency in data exchange
Concluding remarks

- REACH sets the standard information requirements as baseline

- Huge opportunities for use of alternative information and ITSs but……..

- Information must provide a sound basis for managing risks to human health and the environment

- Need for communication and collaboration between regulators, researchers and industry to achieve progress and consensus on use of alternative information in a regulatory context
Thank you!