‘Integrated Testing Strategies’ for REACH

Perspective from the European Chemicals Agency

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Outline

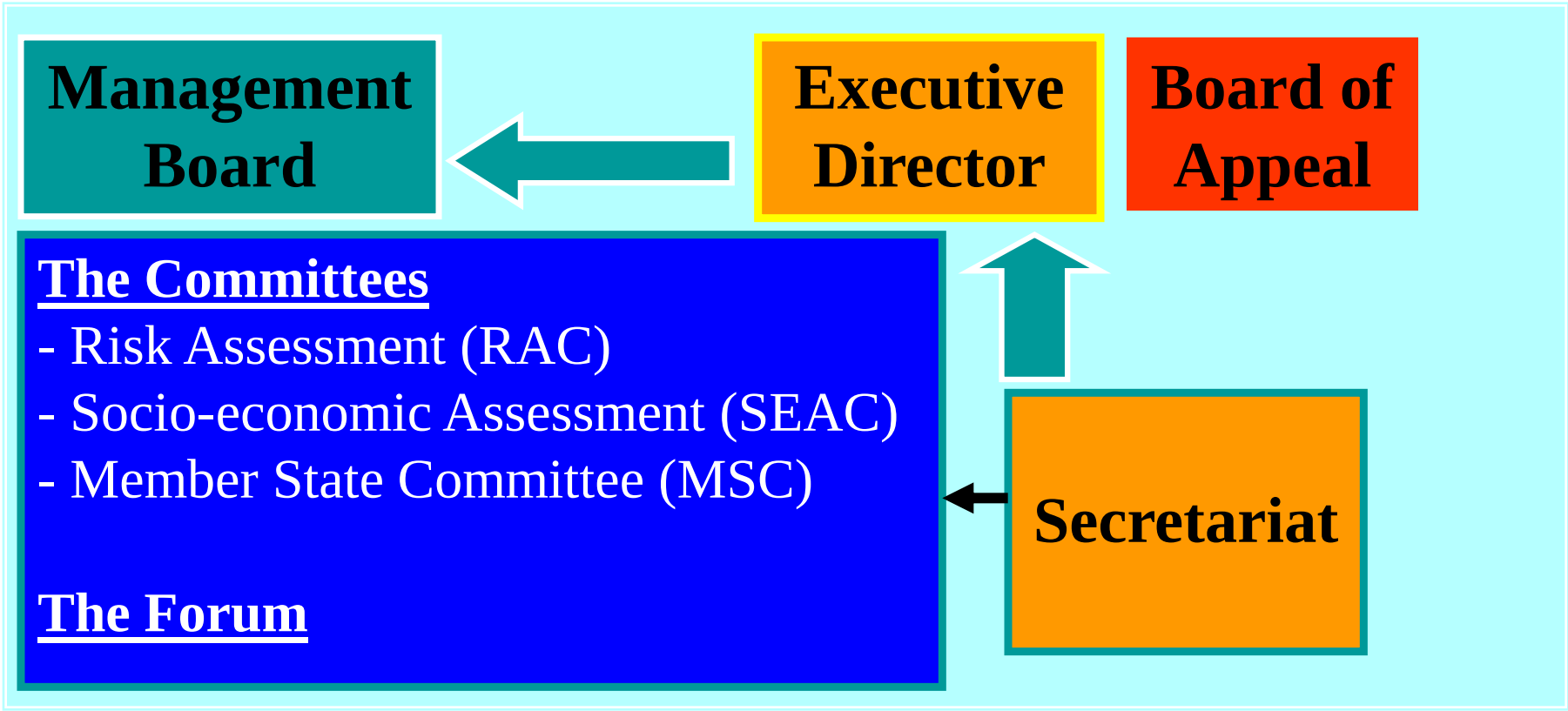
- ECHA mission and role
- Registration and information requirements
- Need for ‘Intelligent’ (integrated) testing strategies
- Further necessary developments

Establishment of the European Chemicals Agency (ECHA) and its mission

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

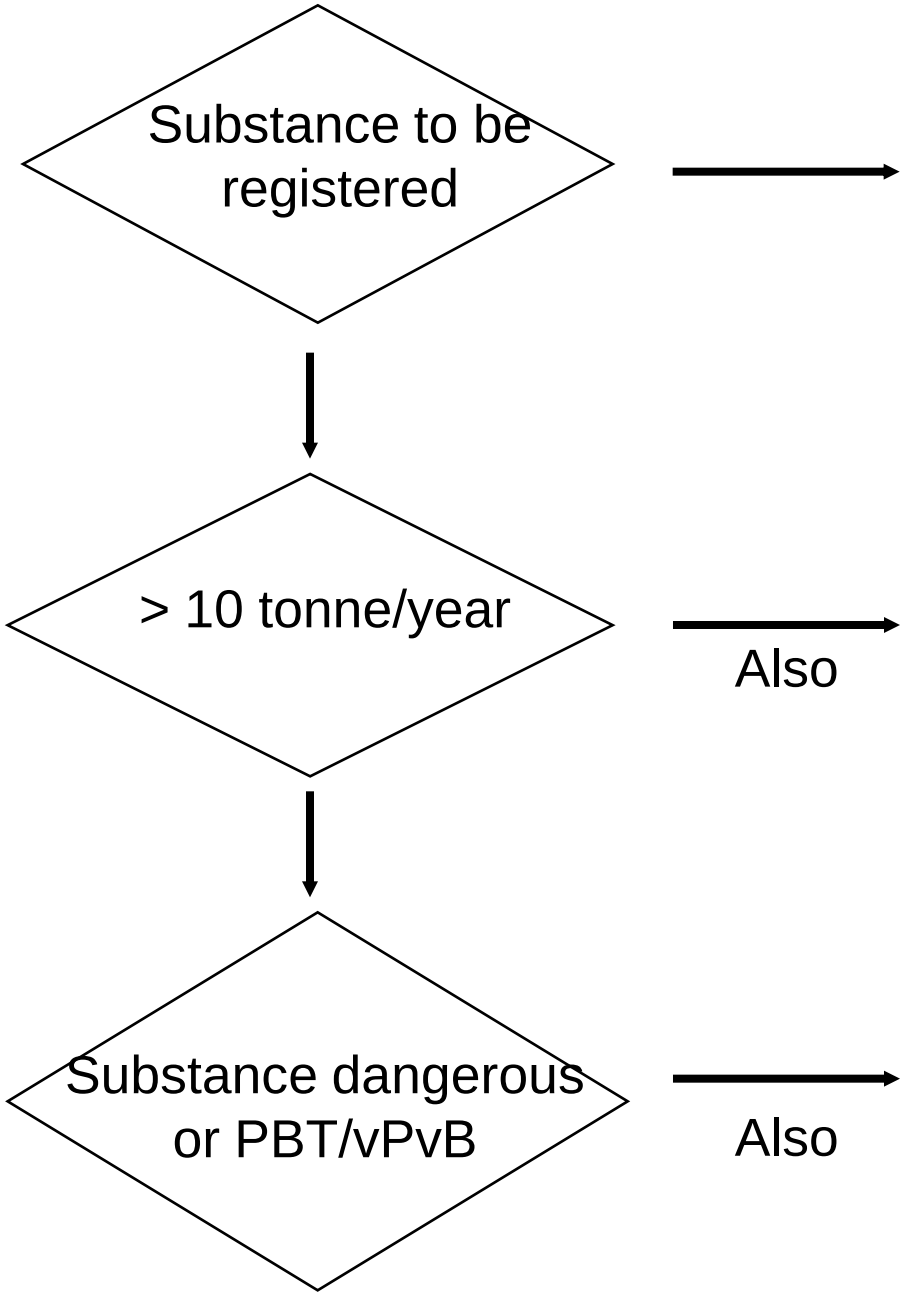
- Manage all REACH related tasks by carrying out or coordinating the necessary activities, in order to ensure **consistent implementation** at Community level
- To provide the best possible **scientific advice** on questions related to the safety and socio-economic aspects of the use of chemicals
- by 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



REGISTRATION AND INFORMATION REQUIREMENTS

Registration dossier - content



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

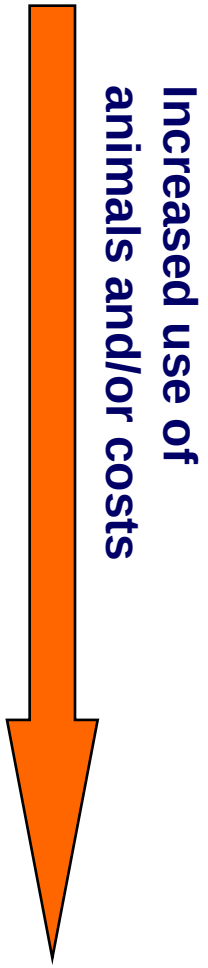
- Hazard and PBT Assessment

Chemical Safety Report

- Hazard and PBT Assessment
- Exposure Assessment
- Risk Characterisation AND
- *Exposure Scenarios*

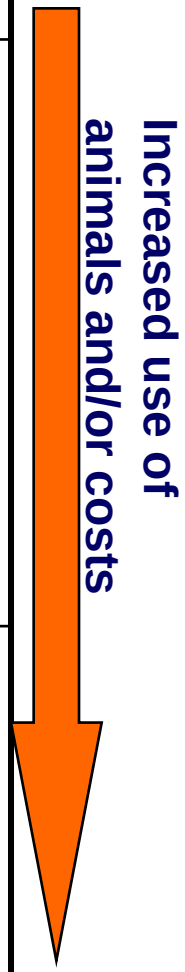
Information requirements

Annex	Human Health	Environment
Annex VII (≥ 1 tpa)	•*In vitro* skin and eye irritation •Skin sensitisation •*In vitro* mutagenicity •Acute toxicity (one route)	•Short term toxicity (daphnia, algae) •Degradation (biotic)
Annex VIII (≥ 10 tpa)	•*In vivo* skin and eye irritation •Further *in vitro* mutagenicity •Acute toxicity (2nd route) •Short-term RdT (28 days) •Reproductive toxicity screening •Assessment of toxicokinetics (not a testing requirement)	•Short term toxicity (fish) •Respiration inhibition test •Degradation (hydrolysis) •Fate (absorption/desorption)



Information requirements

Annex	Human Health	Environment
Annex IX (≥ 100 tpa)	•Further *in vivo* mutagenicity studies (if + results) •Sub-chronic toxicity (90-days) •Reproductive toxicity tests	•Long-term toxicity (invertebrates, fish) •Biotic degradation (simulation studies) •Identification of degradation products •Fate: bioaccumulation in fish, further absorption/desorption •Short term toxicity- terrestrial organisms (invertebrates, MO, plants)
Annex X (≥ 1000 tpa)	•Further *in vivo* mutagenicity studies (if + results) •Further reproductive toxicity studies • *Chronic toxicity (may)* • *Carcinogenicity (may)*	•Further biotic degradation •Further fate •Long-term effects on terrestrial organisms •Long-term or reproductive toxicity to birds



Article 13

“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?

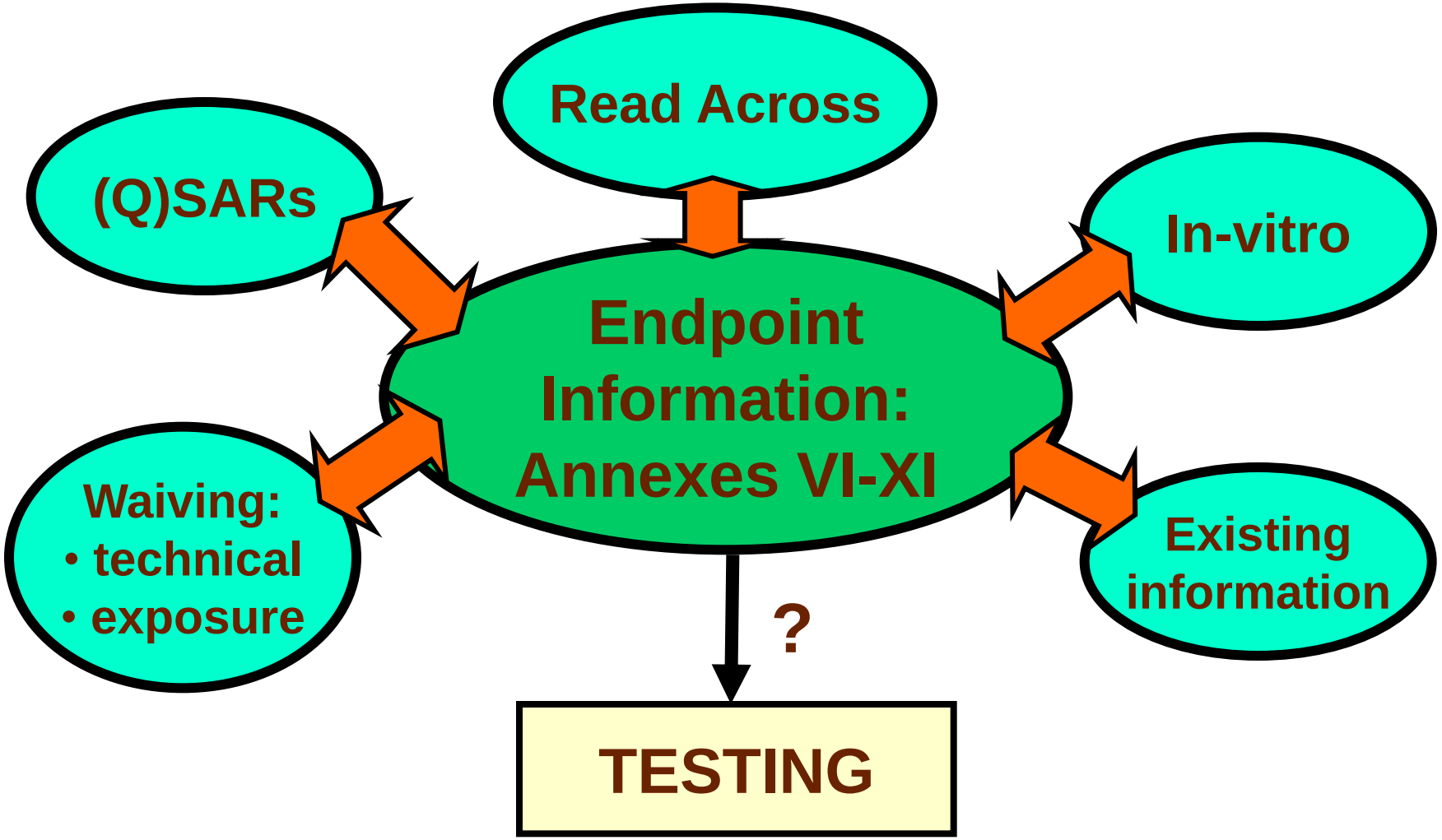
Need for Integrated/Intelligent Testing Strategies!

- 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”

Elements of Integrated testing strategies



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!