Legislative overview on the use of alternative methods in REACH

CADASTER Workshop on the use of QSAR models in REACH

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ECHA – Evaluation

Outline

- Introduction (registration and information requirements)
- Legislative overview for the use of alternative methods
- Experience so far

NF1

Aim of the REACH Regulation (EC No 1907/2006)

- Article 1 (1): *The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods of assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation.*

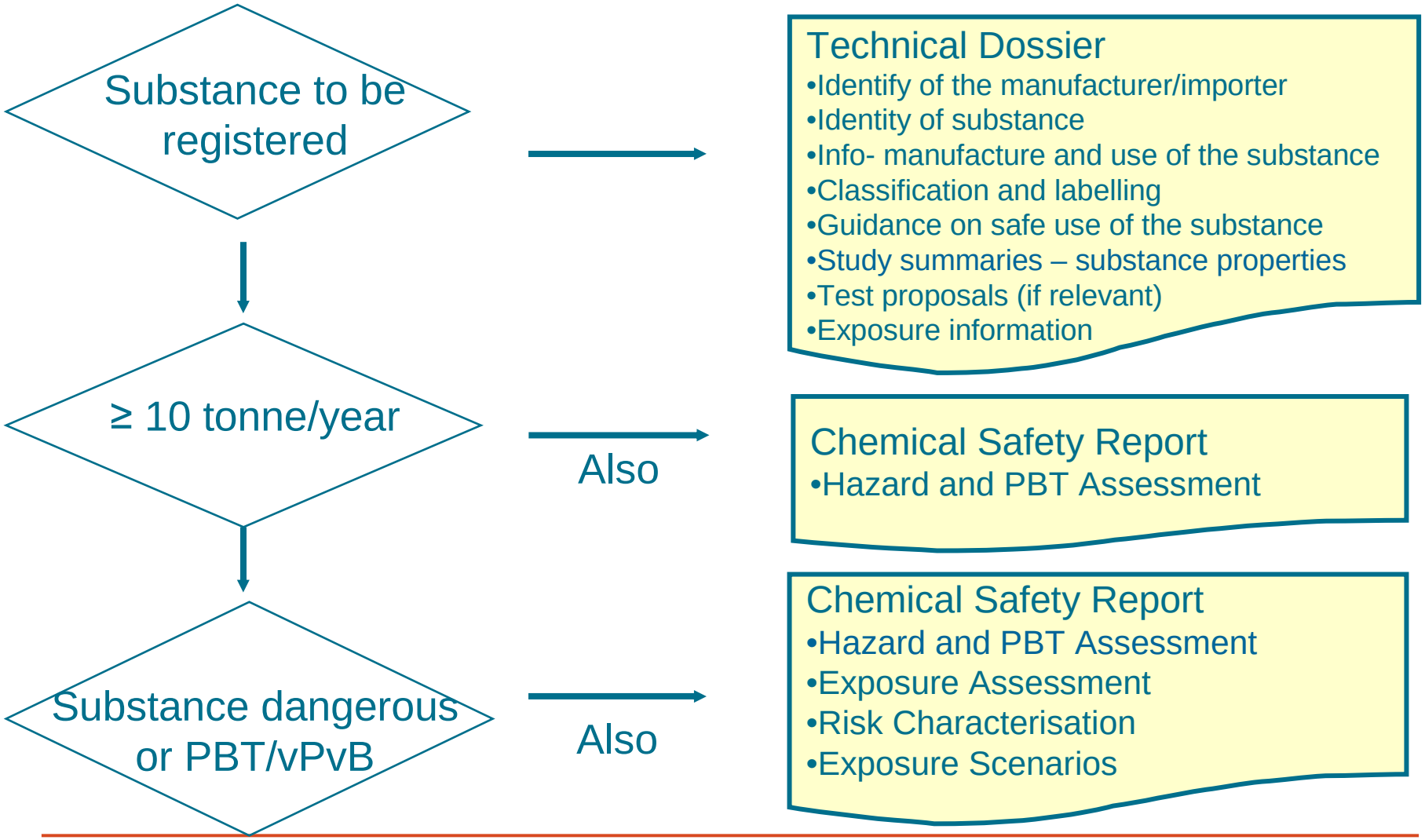
Slide 3

NF1 I would not highlight here. This gives the impresion from the start that the 'inclusing par't is the more relevant one. In the oral I would emphasise the conflicting goals the first two purposes represent and that your talk adresses how the REACH regulation has implemented these.
Norbert Fedtke, 24/08/2011

Registration and information requirements

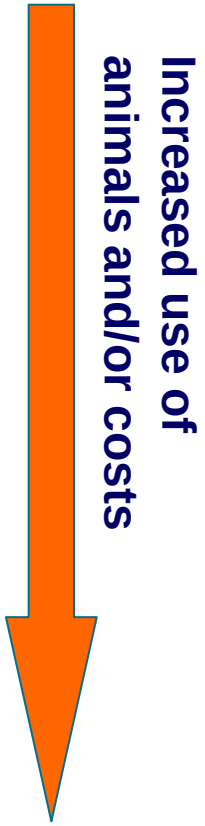
- Manufacturers and importers of a substance on its own or in mixtures in quantities ≥ 1 t/a (Article 6(1));
- Producers or importers of articles under conditions in Article 7;
- Staggered information requirements (Annex VI-X), depending on the tonnage;
- Staggered registration deadlines for phase-in substances;
- The registrant must be able to demonstrate using scientifically reliable data that their chemicals can be used safely.

Registration dossier - content



Standard 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)**



Standard 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**

Increased use of animals and/or costs

Meeting the information requirements 4 steps:

1. Gather and share existing information

2. Consider information needs (Annex VII-X)
   - specific criteria for adaptation in column 2 of Annexes VII-X for specific endpoints
   - general criteria for adaptation in Annex XI

3. Identify information gaps

4. Generate new data/Propose test

Need for Integrated Testing Strategies (ITSs)!

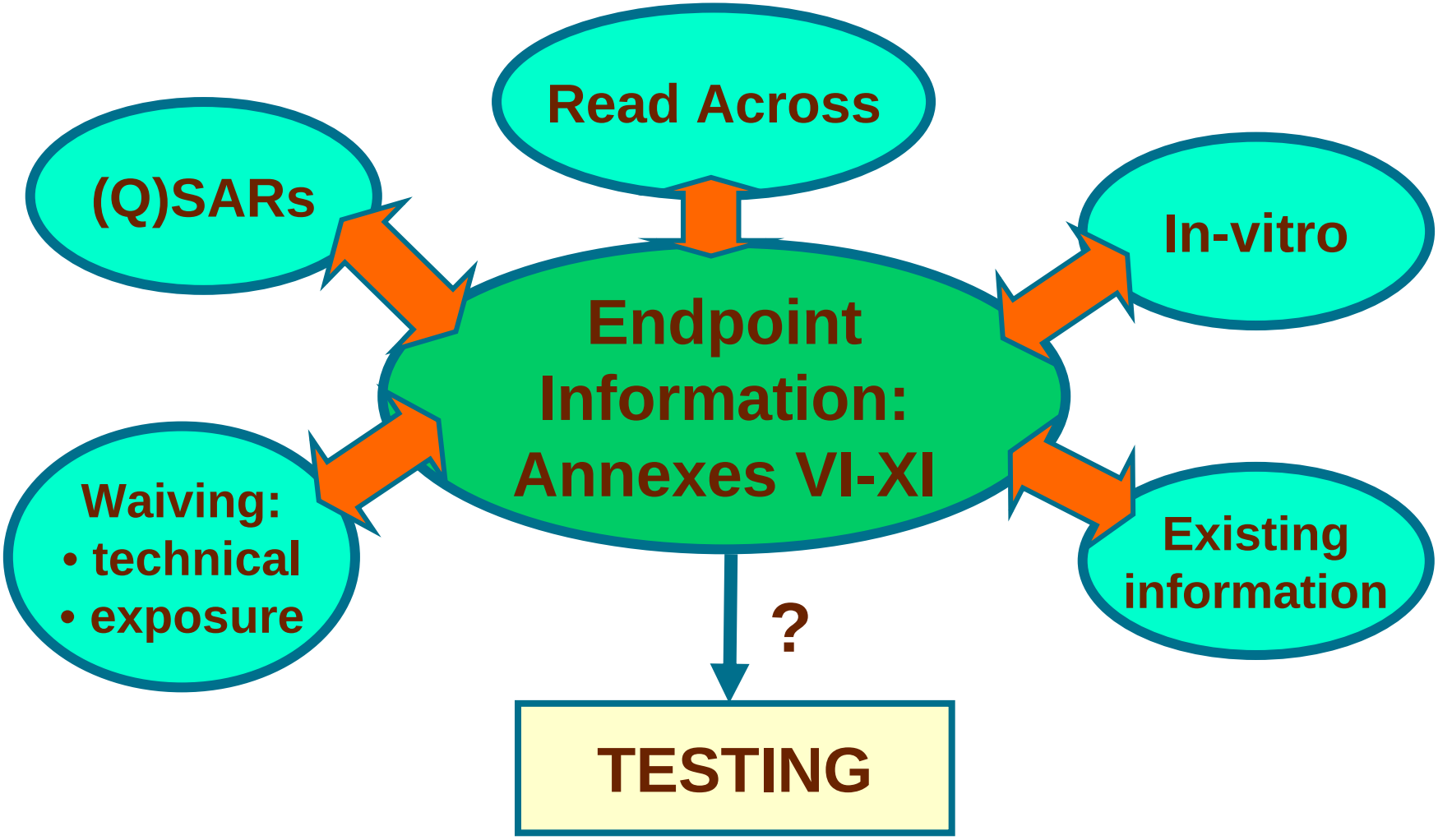
- To get the “right information” to adequately identify and manage the risks
- To limit the number of animal tests
- To reduce the costs for industry
- To speed up the assessment process

- Extensive guidance developed with stakeholders involvement:

“Guidance on information requirements & Chemical Safety Assessment”

http://guidance.echa.europa.eu/guidance_en.htm

Elements of Integrated testing strategies



Legal basis in REACH for the use of alternative methods

Article 13(1):

"Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions of Annex XI are met."

Article 25(1):

"In order to avoid animal testing, testing on vertebrate animals for the purpose of this Regulation shall be undertaken only as a last resort"

Annex VII-X:

"Before new tests are carried out to determine the properties listed in this Annex, all available in vitro data, in vivo data, historical human data, data from valid (Q)SARs and data from structurally related substances (read-across) approach shall be assessed first."

Annex XI: General provisions for adaptation of the standard information requirements

- 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

Adaptation is 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;
  - information needs to be adequate for classification and labelling (C&L) and risk assessment (RA);
  - adequacy and reliability of documentation.

- Industries' responsibility to decide and justify which further information they consider necessary (starting from a minimum data set).

Annex XI: QSAR

Results obtained from valid QSARs may indicate the **presence** or **absence** of a certain dangerous property and may be used instead of testing if:

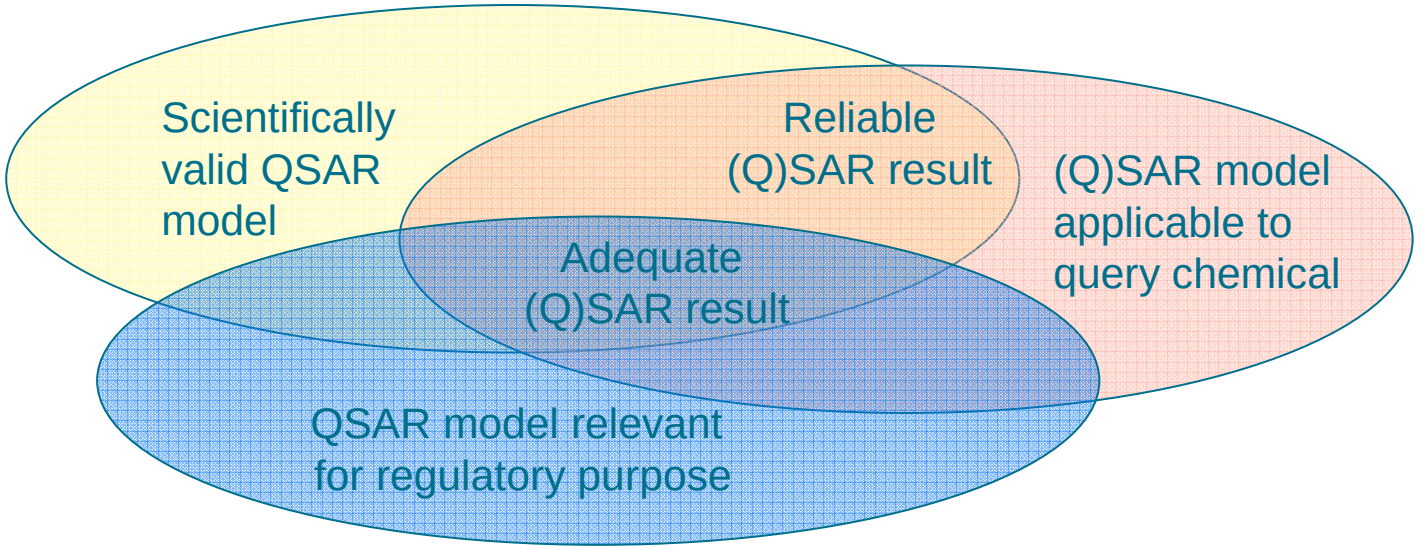
- results are derived from a model whose scientific validity has been established;
- the substance falls within the applicability domain of the model;
- results are adequate for C&L and/or RA;
- adequate and reliable documentation of the applied method is provided.

"Guidance on information requirements & Chemical Safety Assessment: Chapter R.6"

http://guidance.echa.europa.eu/guidance_en.htm

ECHA Guidance on use of (Q)SARs

The **adequacy** of a (Q)SAR prediction for regulatory purposes is related to the model **validity and applicability** to a given chemical, as well as to the model relevance for a regulatory purpose. The validity and applicability together determine the (Q)SAR **reliability**.



Annex XI: Grouping of substances and read-across

- Substances whose **physicochemical**, **toxicological** and **ecotoxicological properties** are **likely to be similar** or **follow a regular pattern** as a result of structural similarity may be considered as a group, or "category" of substances.

- A requirement that **physicochemical properties, human health and environmental effects and environmental fate may be predicted** from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

Annex XI: Grouping of substances and read-across (II)

- The results should:
  - be adequate for C&L and RA;
  - have adequate and reliable coverage of key parameters addressed in the corresponding test method;
  - cover an exposure duration comparable/longer than the corresponding test method;
  - have adequate and reliable documentation.

"Guidance on information requirements & Chemical Safety Assessment: Chapter R.6"

http://guidance.echa.europa.eu/guidance_en.htm

Experience so far (I)

- Registrants made use of the options available in REACH to use alternative methods;
- Registrants mainly used **existing animal studies** (conducted before REACH), **read-across** and **weight of evidence** to fulfil the information requirements;
- **Computer modelling (QSAR)** was not much used to fulfil the informationrequirements; mostly used for environmental endpoints

ECHA Report (2011): "The Use of Alternatives to Testing on animals for the REACH Regulation"

http://echa.europa.eu/doc/117reports/alternatives_test_animals_2011_en.pdf

Experience so far (II)

- In accordance with Article 41 of REACH, ECHA may within the scope of dossier evaluation carry out a compliance check (CCH) on any registration, to verify whether:
  - the information requirements are adequately fulfilled;
  - the adaptations are adequately justified.

- Based on the CCHs carried out so far, one of the key problems in the registration dossiers is missing or inadequate justifications used for adaptations made for information requirements.

ECHA report (2011): Evaluation progress report

http://echa.europa.eu/publications_en.asp

Experience so far (III): Shortcomings observed in dossiers – (Q)SARs

- Limited information about (Q)SAR model (e.g. version unclear, data on the model not transparent/ available);
- Scientific validity of models not always demonstrated;
- Applicability domain of the models often not analysed (or only partially analysed);
- Not relevant for regulatory purpose (e.g. the endpoint predicted is not suitable to meet the information requirements of REACH).

Experience so far (IV): best practice

- Make convincing cases to provide transparency and allow for independent evaluation:
  - Adaptations from the standard requirements must be based on the provisions of the legal text:
    - Annex XI and/or Annexes VII – X, column 2 of REACH
  - Adequate justification must be provided:
    - Sufficient level of detail required
    - Need for scientific sound case building

ECHA Practical guides

http://echa.europa.eu/publications_en.asp

Concluding remarks

- REACH sets the standard information requirements as baseline

- Opportunities for use of alternative methods/information within ITSs but information must provide sound basis for identifying and managing the risks to human health and environment

- Collaboration between regulators, researchers and industry to achieve progress and consensus on use of alternative information in a regulatory context