# Regulatory Acceptability of Read-Across under REACH

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# Topics of my presentation

- REACH and legal basis for read-across
- Use of read-across by REACH registrants
- ECHA Guidance and Practical Guides
- OECD QSAR Toolbox as a tool for grouping
- Draft read-across assessment framework (RAAF)

# Key messages from REACH

- REACH aims for the high level protection of human health and the environment.
- REACH provides several possibilities for industry to avoid unnecessary animal testing.
- REACH requires that animal testing is used only as a last resort. Tests on vertebrate animals may only be carried out when all other sources of data have been exhausted.
- The development and use of alternative methods is a continuous process.

# One of the alternatives

- One of the alternatives: “Grouping of substances and the read-across approach”;
- This is an “adaptation” of “the standard testing regime” included in Annex XI, 1.5 of the REACH Regulation;
- Next to the following other adaptations:
  - Use of existing data;
  - Weight of evidence;
  - Qualitative and quantitative structure–activity relationship;
  - *In vitro* methods.

# Annex XI, 1.5 or the legal basis I

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.

**AND**

Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data from reference substances within the group by interpolation to other substances in the group (read-across approach).

# Annex XI, 1.5 or the legal basis II

**AND**

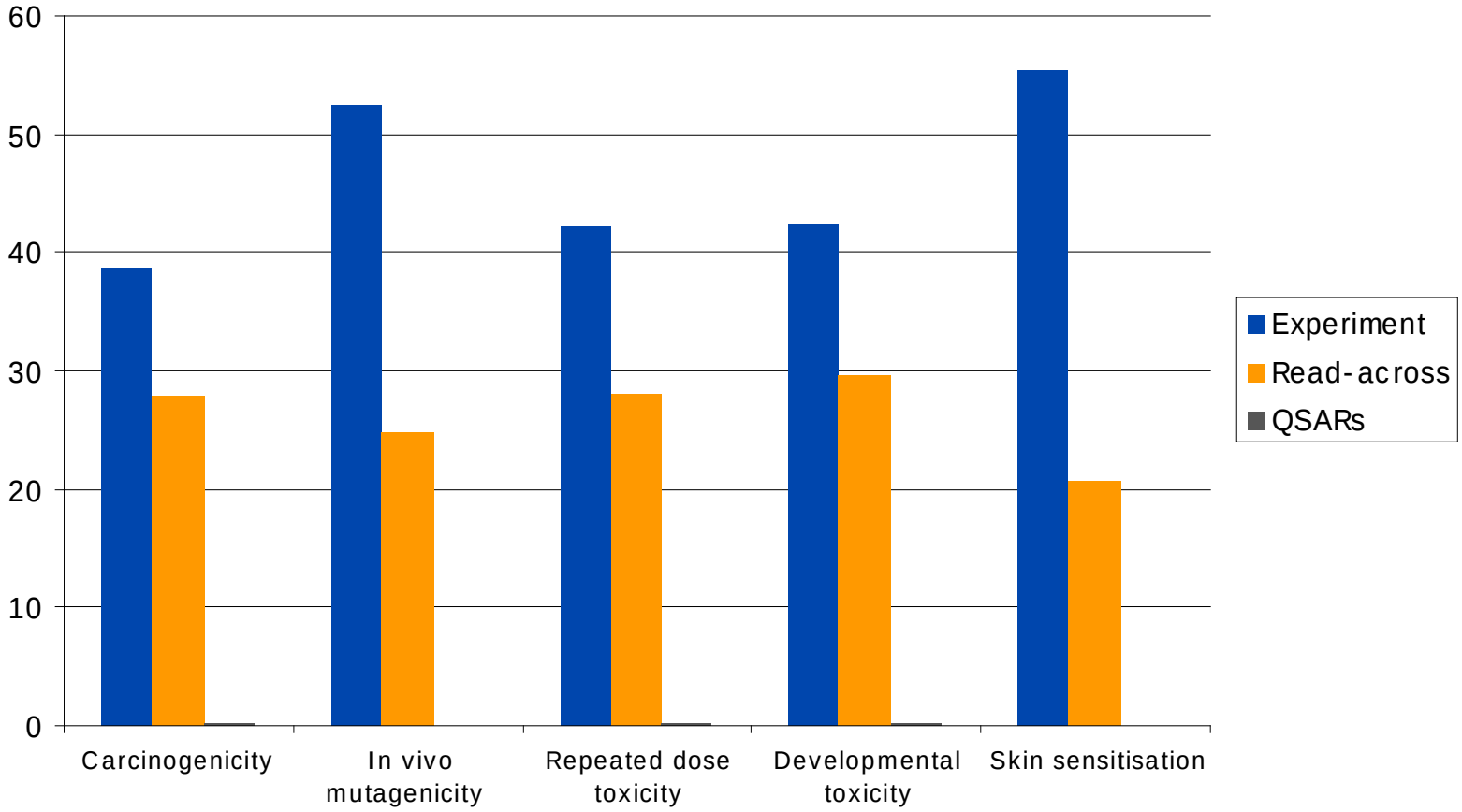
In all cases the results should:

- Be adequate for the purpose of classification and labelling and/or risk assessment;
- Have adequate and reliable coverage of the key parameters addressed in the corresponding test method;
- Cover an exposure duration comparable to or longer than the corresponding test method;
- Adequate and reliable documentation of the applied method shall be provided.

# Data analysis after the first REACH registration deadline

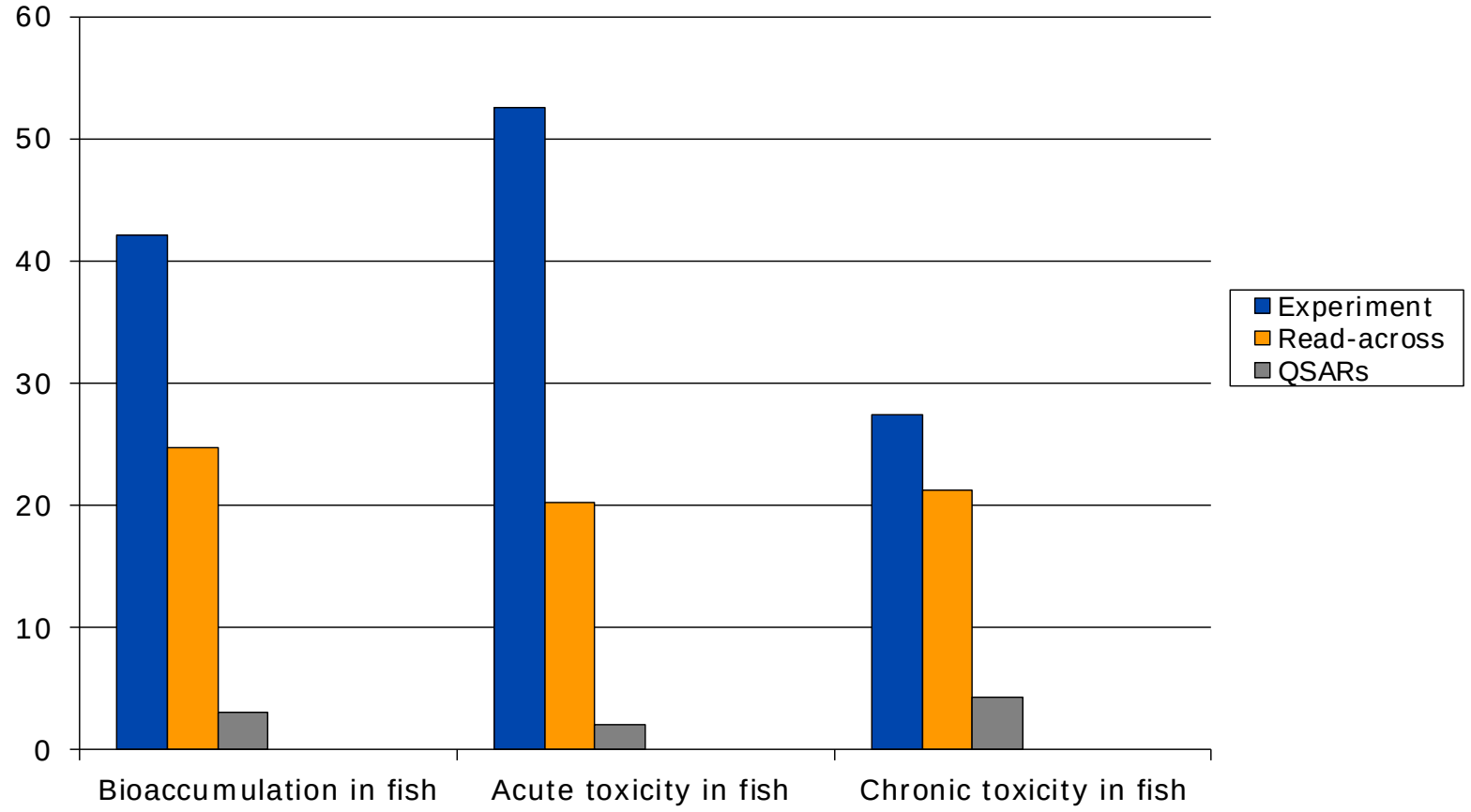
- Sharing information on animal testing worked well - nearly 90% of registrants submitted the information jointly with other registrants for the first REACH deadline.
- Registrants mainly used animal studies that had already been conducted before REACH.
- Predicting the properties of substances by read-across was the next most common means of fulfilling information requirements.

# Results from the data analysis I




http://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2011_summary_en.pdf

# Results from the data analysis II

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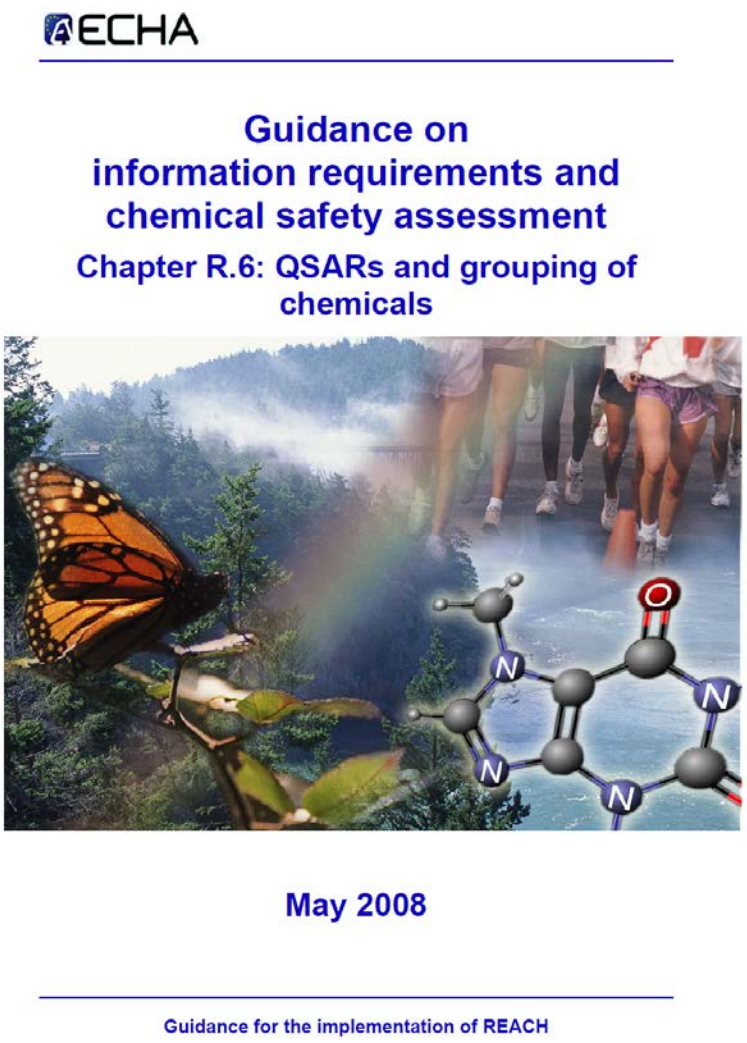
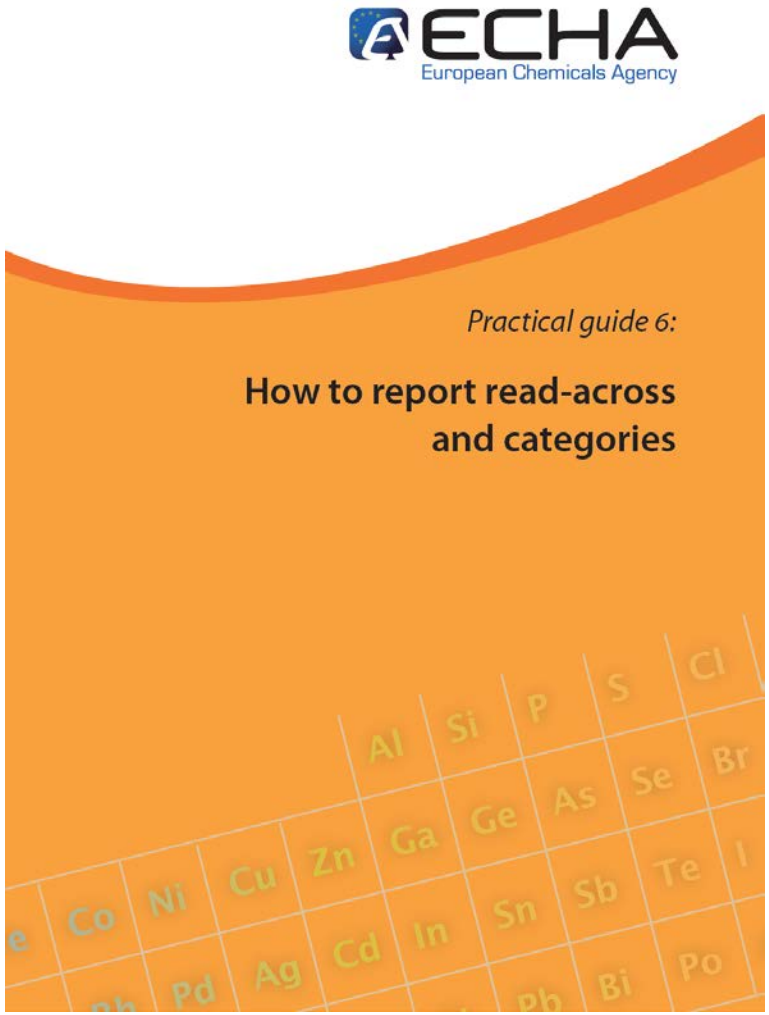
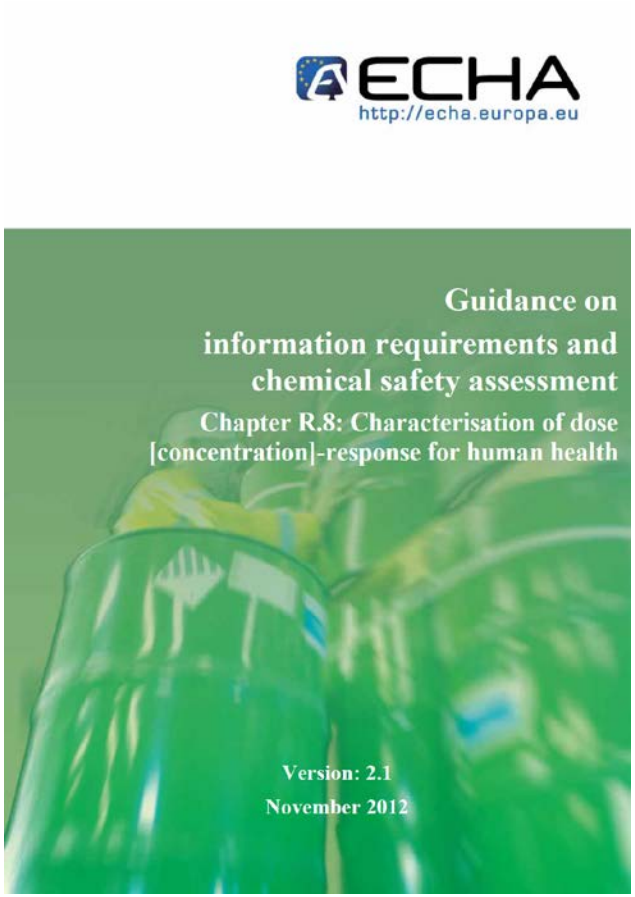
# Guidance and practical guides



"Special consideration should also be given to alternative data, e.g. in vitro data, (Q)SAR, read across or chemical categories. The use of alternative data is stimulated under REACH and preferred above performing additional animal studies, if considered justified. However, using these data in a quantitative way (if at all possible) might be associated with some additional uncertainty in the dose descriptor derived (see Chapter R.7 and general guidance on (Q)SARs and grouping of chemicals (Chapter R.6)). This should be accounted for."



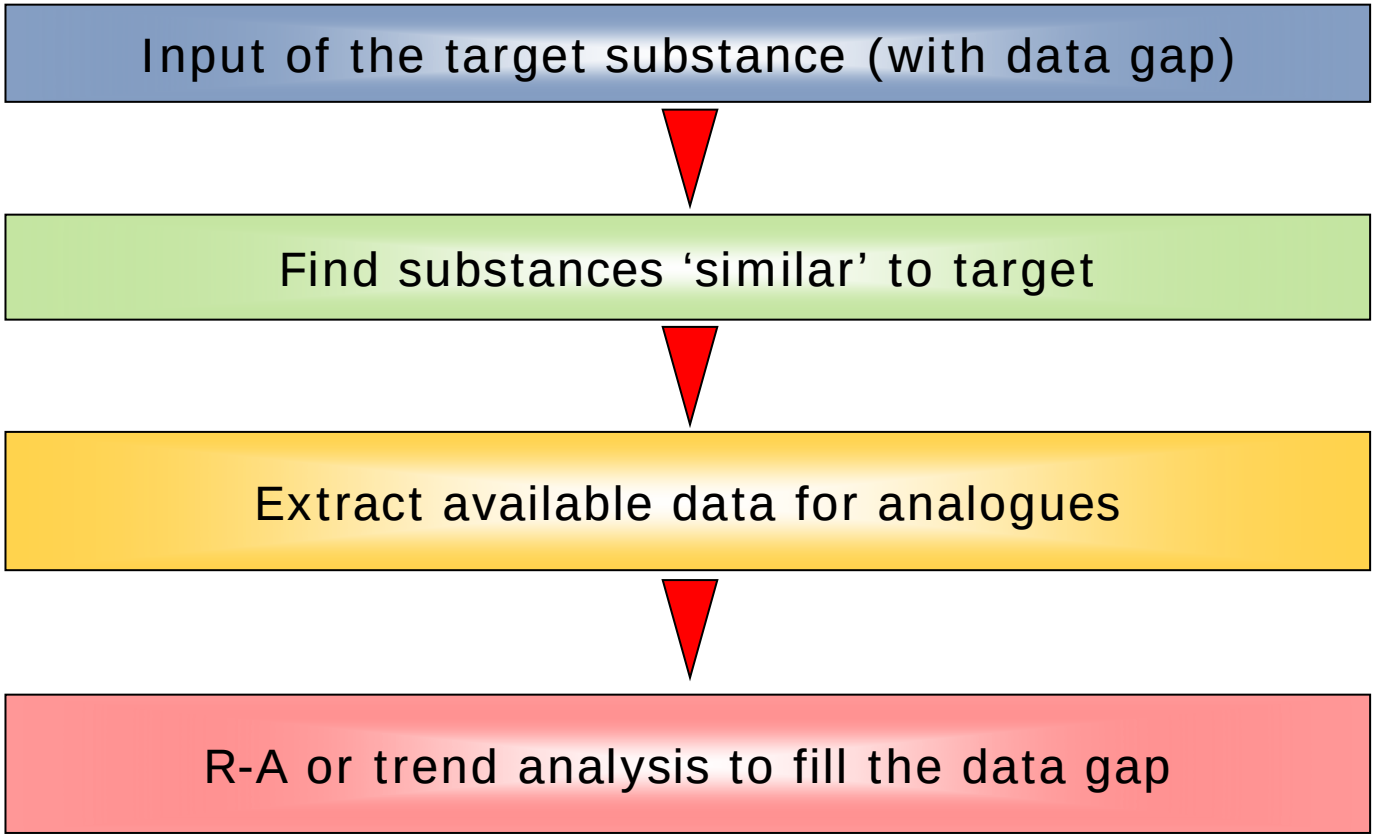
# Read-across and uncertainty

- Read-across introduces **extra** uncertainty!
- The data requirement is normally met by means of an experimental study (e.g. an oral 90-day study, rats)
- Extra uncertainty introduced by read-across:
  - translation from an experimental study with a similar substance to the experimental study with the registered substance.
- REACH Guidance (Chapter R.8, DN(M)EL): If the starting point has been derived by using read-across from one or more structural analogues, the **additional uncertainty** deriving from using these data **may be addressed** by selecting an **additional assessment factor**.

# Some practical considerations

- Substance identity is an important issue;
- Definition starts with structural similarity;
- It should always be explained **WHY** the structural similarity goes with another similarity;
- Such an explanation has nearly always a mechanistic character;
- It often needs support by dedicated studies;
- Sometimes observed trends may on their own warrant data-gap filling, without mechanistic explanation;
- For many explanations the availability of toxicokinetic information is absolutely crucial.

# The OECD QSAR Toolbox workflow



# New approach data to support read-across

- Information from *in vitro* molecular screening & 'omics' assays & computational models can be used to improve the robustness of the read-across case.
  - Either empirically as a common 'signature' for target and source substances.
- Use of the known toxicological profile of the source substance to choose assays pertinent for the relevant biological pathways.
- 'Safety Evaluation Ultimately Replacing Animal Testing' (SEURAT-1) plan a 'read-across' case study.
- Planned ORISE 'Research Project on Chemical Categories Assessment and Refinement' by EPA National Center of Computational Toxicology in collaboration with ECHA.

# Need for a framework

- ECHA needs a tool to achieve consistent, streamlined and transparent evaluation at the high level of expertise required by read-across;
- This framework is designed as a structured tool for the evaluation of read-across cases by the ECHA evaluators.
- Combines practical aspects with expert judgement.
- Intended to calibrate the assessment by hypothesis-driven analysis of read-across and selection of critical aspects

# Structure of RAAF

## **Tier I.** A screening phase.

- It is decided during this phase whether read-across cases can be processed based on relatively simple criteria.
- These criteria do not touch upon the scientific core of the assessment.

## **Tier II.** Scientific evaluation phase

- A phase which is only entered by read-across cases that have passed Tier I. They are then deemed fit for further assessment by means of expert judgement.
- This phase covers the scientific core of the assessment.

# Questions in Tier I

- Is the read-across main or supporting study?
- If supporting, does it bring additional value?
- Is the substance identity of the source substance(s) clear?
- Are there impurities in the target substance that may affect/change the result?
- Is there coverage of key parameters of the test(s)?
- Is the exposure duration sufficient?
- Is the documentation adequate and reliable?
- Is the justification obviously sound or obviously not?

# Description of Tier II

- Facilitates the assessment by introducing basic scenarios:

  scenario = explanation = read-across hypothesis;
- For each scenario: assessment elements that have to be met for acceptance based on the information provided;
- Scoring how far the conditions have been met;
- Deriving an end score for the scenario from the scores of the conditions belonging to that scenario;
- Decision on acceptance based on the end score;
- In case of acceptance dealing with remaining uncertainty based on the end score.

# Illustrative example for read-across

ECHA has developed an illustrative example of a grouping of substances and read-across approach to support companies to comply with their obligations under REACH.

- Part 1: An Introductory Note - provides background information on read-across including general considerations and addresses shortcomings commonly identified by ECHA
- Part 2: Example 1 - contains an illustrative example for a hypothetical substance intended to outline the level of information and reasoning expected to be provided

# Concluding remarks

- Read-across is an allowed adaptation under REACH
- It was used extensively by registrants already
- Especially useful for long term toxicity endpoints
- However, thorough justification required
- There will be more help available for the next registration deadline

# Thank you!

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