

# Adaptations to information requirements in REACH: read-across, Grouping and Categories

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## Read-Across in the context of REACH

- An information requirement of REACH for a certain substance is not met by means of a standard study with the registered substance;
- However, data are available for one or more other substances that are similar in some aspects to the substance for which a registration dossier is prepared;
- It is claimed by the registrant that the data obtained with the **other substances** can be used to meet the information requirement for the **registered substance**;
- In other words, **read-across** is done from the **other substances** to the **registered substance**.

## Facility offered by REACH

- Covered by Annex XI of the REACH Regulation
  - *General rules for adaptation of the standard testing regime set out in Annexes VII to X*
- Section 1.5.
  - **Grouping** of substances and **read-across** approach
  - Substances with physicochemical, toxicological and ecotoxicological properties that 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.
- Application of the **group concept** requires that physicochemical properties, human health effects and environmental effects or 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, 1.5 (1)

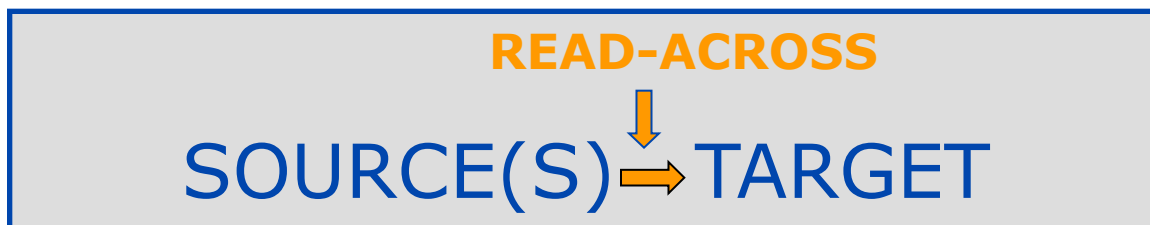
- The similarities may be based on:
  - 1) a common functional group;
  - 2) the common precursors and/or the likelihood of common **breakdown** products via physical and biological processes, which result in structurally similar chemicals; or
  - 3) a constant pattern in the changing of the potency of the properties across the category.
- If the group concept is applied, substances shall be classified and labelled on this basis.

## Annex XI, 1.5 (2)

- In all cases, 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 referred to in Article 13(3),
  - cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and
  - adequate and reliable documentation of the applied method shall be provided.

## Source and target substances

- The other substances are called **source substances**; they are the source of the data that is used to fill the data gap.
- The substance for which the REACH-registration dossier is prepared is called the **target substance**; the read-across is targeted at this substance; this means that its REACH requirement is met by means of data obtained with the **source substances**.



## Groups and Categories (1)

- A “group” is a number of chemicals that, due to their similarity are expected to have similar REACH-relevant properties. (Not necessarily all REACH-relevant properties!)
- A “category” is a “group” that shows a certain **trend** when a **chemical descriptor** or **physical chemical property** are plotted against a **REACH-relevant property**, for instance oral repeated-dose toxicity in rats.
- Trends can be increasing, constant or decreasing, linear or non-linear.

## Groups and Categories (2)

- Read-across can be done to fill data-gaps for:
  - 1) Chemicals belonging to a group (these are “just” analogues), and
  - 2) Chemicals belonging to a category.
- In the case of a **category**, the trend provides **extra predictive power**. So, read-across for the endpoint is stronger in a category.

**Only group?** → Analogue approach read-across.

**Group = category?** → Category approach read-across.

## Important!

- Trends could be established for some endpoints in a group, and not for others;
- It is the registrant's responsibility to analyse the endpoints, for which the category holds;
- Assuming the same trend for all endpoints and all substances in a category is often not credible.

## Groups and Categories (3)

- A group can consist of two or more substances.
- Many substances may be needed to establish a trend.

**No trend → no category!**

## Groups and Categories (4)

- Read-across is strengthened when the responses of source chemicals in a group point in the same direction, while it is obviously weakened if the source chemicals point to different directions.
- **Many-to-one read-across is better practice than one-to-many.**
- The number of targets that can be covered by one source depends on the strength of the read-across.

## Groups and Categories (5)

- Read-across from one source to many targets has the undesirable effect that it multiplies uncertainty over many hazard assessments.
- It is better to test a number of additional sources, so as to come to a better prediction of the hazards.

## Read-across (1)

- Read-across introduces **extra** uncertainty!
- The data requirement is normally met by means of an experimental study (for instance an oral 90-day study with 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: this uncertainty is to be addressed by means of extra uncertainty factor (AF) during DNEL derivation; **at least 2**.

## Read-across (2)

- Read-across means that properties are predicted and not directly measured.
- **The registrant** has to explain why this is possible; **not ECHA**.
- So the core of every read-across proposal, whether based on groups or on categories, should be such an explanation (a.k.a. read-across hypothesis).
- Often, this explanation needs to be supported with experimental data.
- **No sufficient explanation, no acceptance!**

## Possible supporting data

- Depends obviously on the explanation.
- Data on the absorption, distribution, metabolism, excretion and elimination of source and/or target; toxicokinetics or ADME.
- *In vitro* data that are related to the effect for which read-across is proposed.
- *In silico* investigations.
- Data for other REACH-relevant properties.

Any scientific evidence that really enhances the credibility of the read-across explanation

**Scientific credibility is  
crucial**

**Registrants should always make their case!**

## Part of the Legal Text:

- **Adequate and reliable documentation of the applied method shall be provided**



## **Structural Similarity = Basis of Read-Across**

- The identity of a substance is defined by structures, composition and so-called chemical descriptors.

The statement “these chemicals are similar” has no meaning in the context of REACH.

## Core of every RA explanation

- What makes the source and target structurally **similar** and how is that related to the endpoint for which a data-gap has to be filled by means of read-across;
- What makes the source and target structurally **dissimilar** and how does that affect the possibilities to read-across

## Possible Read-Across “Explanations” (1)

- **Trend analysis combined with a mechanistic explanation;**
  - e.g., there is also a credible explanation as to why and how the category-defining property (for instance number of C-atoms) relates to the REACH-relevant property (for instance repeated dose toxicity in rats after 90 days of oral exposure);
- **Trend analysis only** - if the trend in a category is strong and reliable.

## Possible Read-Across “Explanations” (2)

- **Trends in other endpoints** than the endpoint for which a data-gap has to be filled.
  - For instance, when many other toxicological parameters show a clear common trend, it may be reasoned that the read-across endpoint will follow the same trend. This explanation often has to be combined with other explanations, for instance explanations based on mechanistic considerations.
- Formation of **identical metabolites/ chemical transformation products** and **equal exposure** of the sensitive organs/tissues.
- Source and target or their metabolites are similar enough to have **similar effects and kinetics**.

## Worst-case approach

- Depending on the role of the outcome of read-across in hazard assessment, a worst-case approach can be followed.
- In some cases, it is possible to argue that the source will anyhow be more toxic than the target.
- An underestimation of a hazard is then prevented.
- Is the overestimation acceptable?
- What if the read-across is not conservative enough and there is an underestimation of a hazard?

## Identity of substances

- The validity of read-across may be affected by the composition of, and impurities in the source and/or target;
- In particular, if impurities in the target contribute to the toxicity while they are not present in the source.

# Evaluation of Read-Across Proposals

- Depends on the role of the read-across in the REACH registration dossier;
  - it can be part of a weight of evidence analysis;
  - its purpose can also be to meet an entire information requirement;
  - is it qualitative or quantitative?
  - it can be part of an integrated testing strategy.
- **Many cases are rejected because essential information is lacking;**
- **Quality of the explanation and the supporting data play a crucial role in ECHA's evaluation;**
- The evaluation is ultimately based on expert judgement;
- Uncertainty or lack of quality may be compensated for by extra uncertainty factors and thus by lower DNELs.

## Supporting data

- Supporting data needs to be present in the dossier and not just referred to;
- This also holds for literature data; literature data can play an important role in underpinning to read-across.

## Guidance

- Guidance on information requirements and chemical safety assessment; Volume 8: Chapter R.6: QSARs and grouping of chemicals:
  - [http://echa.europa.eu/documents/10162/17224/information\\_requirements\\_r6\\_en.pdf](http://echa.europa.eu/documents/10162/17224/information_requirements_r6_en.pdf)
- Practical guide 6: How to report read-across and categories
  - [http://echa.europa.eu/documents/10162/17250/pg\\_report\\_read\\_across\\_en.pdf](http://echa.europa.eu/documents/10162/17250/pg_report_read_across_en.pdf)

**Following this guidance ensures your read-across proposal receives all the attention it deserves**

# Thank You

<http://echa.europa.eu/>

