

How to bring your registration dossier in compliance with REACH

Tips and Hints - Part 5

Read-across

Niklas Andersson

12 February

Read-across - Definition

- Read-across is a technique for **predicting** endpoint information for one substance (**target** substance), by using data from the same endpoint from (an)other substance(s), (**source** substance(s)).
- One-to-one
- One-to-many
- Many-to-one
- Many-to-many

Read-across – in the context of REACH

- Annex XI, section 1.5 “Grouping of substances and read-across approach”: to adapt the standard testing regime of Annex VII to X.
- Annex XI, section 1.2 “Weight of evidence”: read-across may be used as a line of evidence

Whenever read-across is used...

...the REACH Regulation requires that the following conditions are fulfilled:

- “results must 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 or longer than the corresponding method if exposure is a relevant parameter”
- “adequate and reliable documentation of the applied method shall be provided”

General recommendations on use of read-across in REACH registration dossiers



Make a clear read-across hypothesis and justification

- Read-across **hypothesis**:
 - Describes the structural similarities and any other similarities identified
 - Explains why the properties of the target substance can be predicted from data on the source substance(s) **for each endpoint concerned**
- Read-across **justification**:
 - Demonstrates that the hypothesis is supported by referring to a data set: **all claims must be supported by data**
 - Outlines the shortcomings and uncertainty associated with the approach

Provide substance identity information on all substances included in the read-across

All substances included in the read-across must be **unambiguously** identified

For each substance, provide:

- **Identifiers**: EC number, CAS number, CAS/IUPAC name, chemical structure
 - UVCBs: specific rules for naming and identification apply
- **Composition** and **impurity profile**: impact of minor components and/or impurities on toxicity profiles
- **Phase/Form**: impact on the toxicity profiles

Outline the structural similarity(ies) between the substances

Annex XI, section 1.5: *"substances whose physico-chemical, toxicological and ecotoxicological properties are likely to be similar **as a result of structural similarity** may be considered as a group"*

- Assess the **structural similarities** between the source and target substances
- Assess the impact of the **structural differences** on the toxicity profiles/potential of the source and target substances

Read-across hypothesis and justification – in IUCLID

For each endpoint, when the read-across approach includes only one endpoint study record

Report the read-across hypothesis in the field **Rationale for reliability**

Report the read-across justification in the section **Results and discussions**

Attach any relevant document to the endpoint study record

Reliability: 2 (reliable with restrictions)

Rationale for reliability incl. deficiencies: enter the hypothesis for the analogue approach

Results and discussions

Effect concentrations

Duration	Endpoint	Effect conc.
96 h	LC50	1.5 mg/L

Any other information on results incl. tables

Enter the analogue approach justification.
Enter the data matrix with the available experimental results.

Attached background material

Attached document: Reporting format for the analogue approach.doc

Read-across hypothesis and justification – in IUCLID

For each endpoint, when the read-across approach includes more than one endpoint study record – report in **Endpoint Summaries**

The screenshot displays the IUCLID software interface. At the top, a navigation tree shows the following structure:

- Toxicological information
 - 7.1 Toxicokinetics, metabolism and c
 - 7.2 Acute Toxicity
 - Acute Toxicity** (highlighted with a red box)
 - 7.2.1 Acute toxicity: oral

Below the tree, the 'Short description of key information' field is empty. The 'Discussion' section contains a rich text editor with two red-bordered input boxes:

- Enter the read-across justification here.
- Enter the read-across hypothesis here.

At the bottom, the 'Attached background material' section shows a table with one entry:

Attached document
Reporting format for the analogue approach.doc

Below the table are buttons for 'Add...', 'Edit...', 'Delete', and 'Move'.

Provide substance identity information on the test materials

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

no

Test material identity

Identifier	Identity
CAS number	
IUPAC name	

Add... Edit... Delete Move up Move down

Details on test material

1. Describe the source chemical(s) as comprehensible as possible. Include SMILES of the source chemical as well as any other identifiers
2. Provide purity/impurity profiles for the source chemicals, including the likely impact on the relevant endpoints....

Use the related "freetext template" as shown here below

- Name of test material (as cited in study report):
- Molecular formula (if other than submission substance):
- Molecular weight (if other than submission substance):
- Smiles notation (if other than submission substance):
- InChI (if other than submission substance):
- Structural formula attached as image file (if other than submission substance):
- Substance type:
- Physical state:
- Analytical purity:
- Impurities (identity and concentrations):
- Composition of test material, percentage of components:
- Isomers composition:
- Purity test date:
- Lot/batch No.:
- Expiration date of the lot/batch:
- Radiochemical purity (if radiolabelling):
- Specific activity (if radiolabelling):

Confidential details on test material

same as above in case of confidentiality on the source chemical

Source: ECHA practical guide 6 How to report read-across and categories

Toxicological properties: toxicokinetics and metabolism

Toxicokinetic information on the source and target substances can considerably strengthen the robustness of the hypothesis.

- Hypothesis based on same metabolic pathway: **existence, rate and extent** of metabolism
- Is this metabolic pathway the **main biotransformation process**? Impact and relevance of alternative pathways
- **Other metabolites** identified? Assess their toxicity

Support all the claims with data – IUCLID section 7.1

Ecotoxicity properties: quantitative assessment

- The registrant should justify **why the target substance is of equal or less concern/toxicity** than the source substance
- Fate and toxic potency of analogues should be compared by trend analysis or QSAR if possible
- **Qualitative read-across** is appropriate only when it can be demonstrated that quantitative estimations are not needed

Further information on qualitative and quantitative read-across is provided in **REACH guidance R.6**.

Use all available data sources

Consider all sources of data when developing a read-across

- Literature, QSAR: valuable **supporting information**
- Mechanistic information, “omics”: insights on mode of action
- Critically **assess the reliability and adequacy** of this information
 - May not be sufficient as stand alone information for some higher tier endpoints
- Use the **appropriate reporting formats**:
 - Experimental and literature data: (robust) study summaries in IUCLID
 - QSAR data: attach QMRF and/or QPRF to the IUCLID dossier – see ECHA Guidance R6, section 6.1.6.

Useful links

- ECHA Guidance on information requirements and chemical safety assessment R6 -
http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf
- ECHA illustrative example on read-across –
<http://echa.europa.eu/web/guest/support/grouping-of-substances-and-read-across>
- ECHA practical guide 06: how to report read-across and categories -
http://echa.europa.eu/documents/10162/13655/pg_report_readacross_en.pdf
- ECHA practical guide 03: how to report robust study summaries -
http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf
- ECHA Guidance for identification and naming of substances under REACH - http://echa.europa.eu/documents/10162/13643/substance_id_en.pdf
- ECHA Guidance on information requirements and chemical safety assessment R.7(c), section 7.12 Guidance on toxicokinetics -
http://echa.europa.eu/documents/10162/13632/information_requirements_r7c_en.pdf

Questions?

To the Q&A panel (between 11:00 and 13:30, Helsinki time), or

To the ECHA helpdesk (any time):

<http://echa.europa.eu/contact/helpdesk-contact-form>