How to bring your registration dossier in compliance with REACH

Tips and Hints - Part 5

Read-across

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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

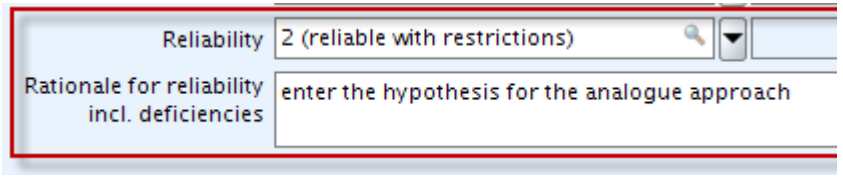
Annex XI, section 1.5: "*substances whose physico-chemical, toxicological and ecotoxicological properties are likely to be similar* ***as a result of structural similarity*** *may be considered as a group*"

- 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

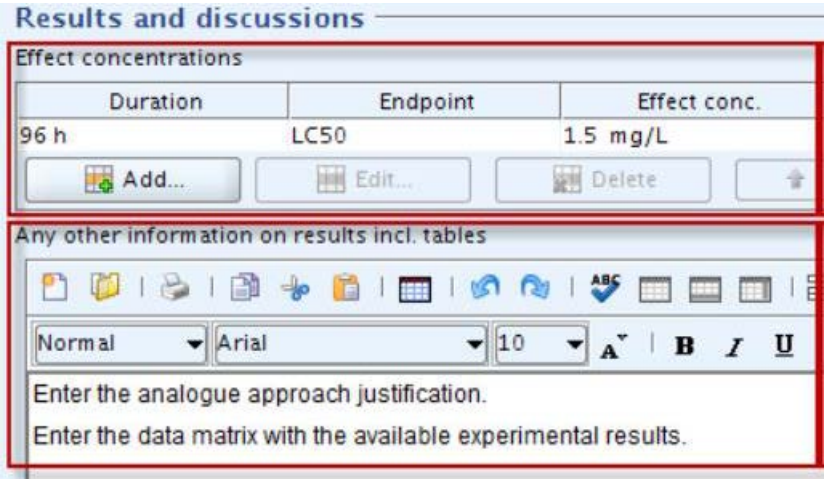
Read-across hypothesis and justification – in IUCLID

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

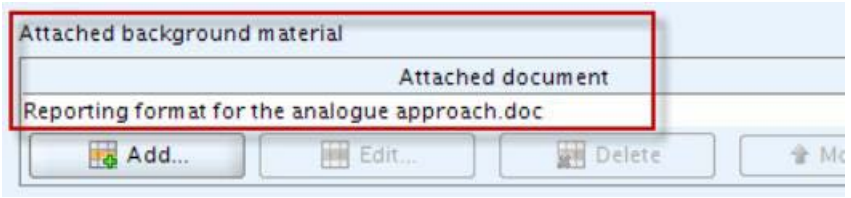
Report the read-across hypothesis in the field **Rationale for reliability**



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

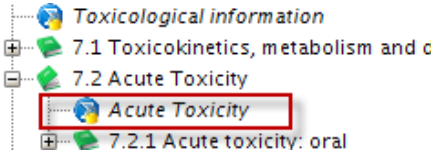


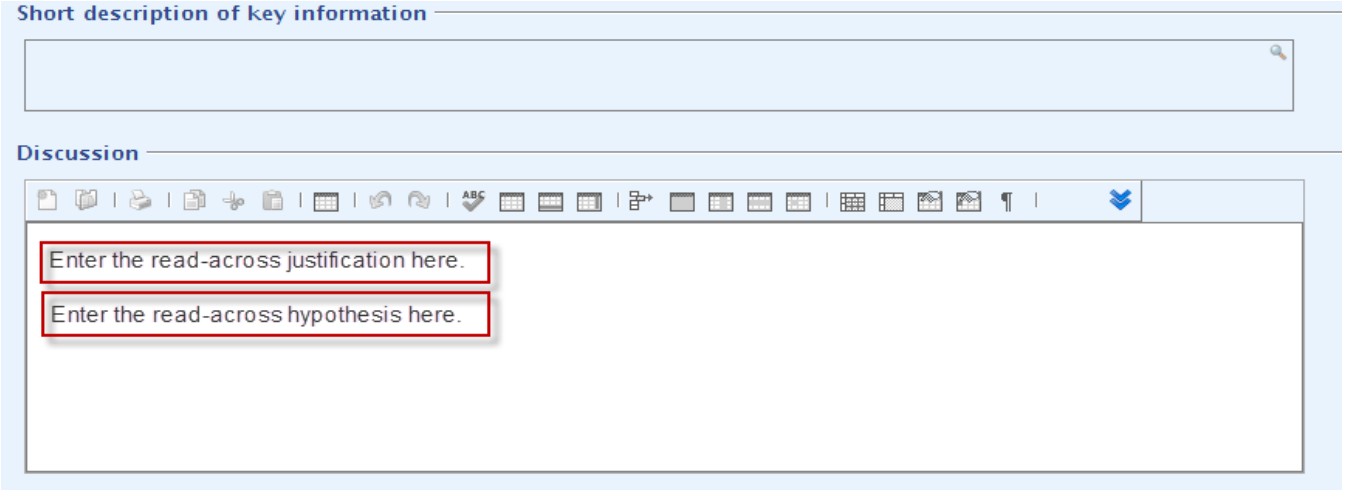
Attach any relevant document to the endpoint study record

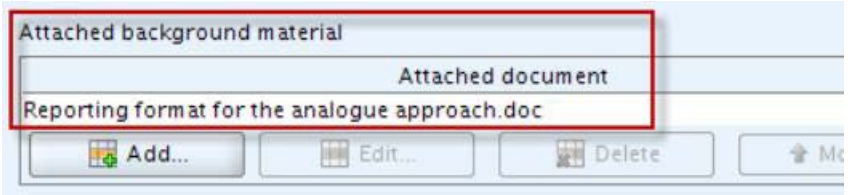


Read-across hypothesis and justification – in IUCLID

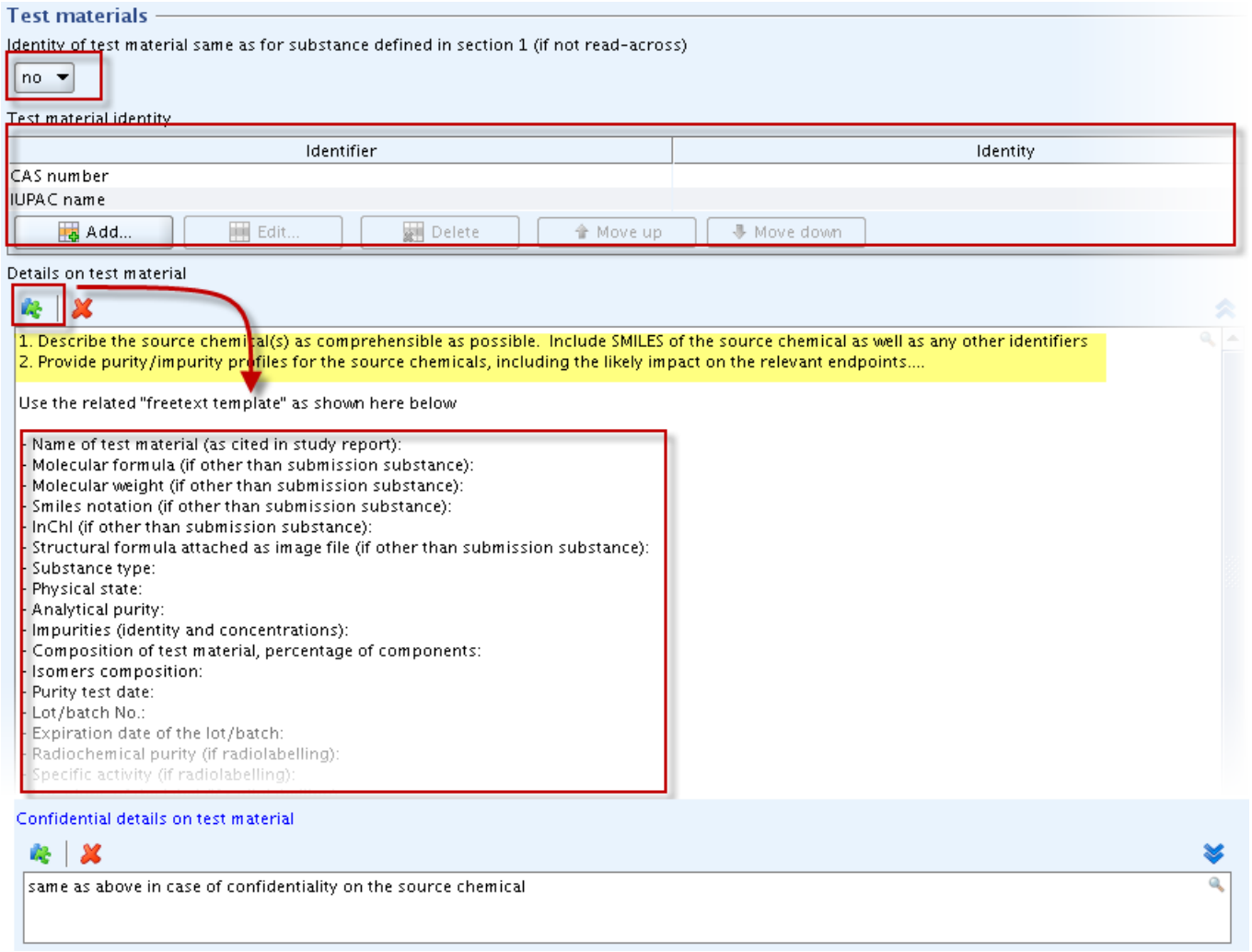
For each endpoint, when the read-across approach includes more than one endpoint study record – report in **Endpoint Summaries**







Provide substance identity information on the test materials



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