ECHA
EUROPEAN CHEMICALS AGENCY

Grouping of substances and read-across approach

Part 1: Introductory note

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Grouping of substances and read-across approach – an illustrative example

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Table of Contents

1. Introduction

The objectives of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) are set out in its preamble, including recitals 1 and 38, and in Article 13, which all underline the need to generate data by means other than tests whenever this is possible. Annex XI, 1.5 of REACH sets the conditions/criteria for using grouping and read-across approaches under REACH to fulfil the information requirements.

If the read-across approach is adequate, unnecessary testing can be avoided. A read-across approach can also support a conclusion for a REACH endpoint using a weight-of-evidence approach.

This publication has two sections: Part 1, an introductory note, which provides background information on read-across including general considerations; and Part 2, which contains an illustrative example for a hypothetical substance. Additional examples will be added to Part 2 in the future.

The introductory note and illustrative example address shortcomings commonly identified by ECHA when evaluating registration dossiers submitted to the Agency. The example shows the level of information expected to be provided and includes explanatory comments, which expand on the reasoning and approach taken.

ECHA aims to support industry to improve the quality of the information provided in their registration dossiers. This applies both to updates of existing grouping of substances and read-across approaches, and to such approaches being prepared for the future registration deadlines of 1 June 2013 and 1 June 2018 or for new registrations.

The objective of this introductory note and example is to illustrate:

- The nature and content of information required to document and support the grouping of substances and read-across approach according to the requirements of Annex XI section 1.5 of the REACH Regulation.
- How to reason that the prediction of substance properties, using read-across, leads to adequate and reliable results for each endpoint under consideration.
- How to improve the quality and consistency of the grouping of substances or analogue approaches and to resolve common shortcomings identified by ECHA when evaluating the dossiers.

2. Background and definitions

The practice of predicting properties of chemicals is already established in regulatory science, and improved techniques are evolving as scientific knowledge develops and is applied to this field. In view of the widespread use in different regulatory schemes and for different purposes as well as the changes over time, there is a potential for misunderstanding by REACH registrants. Therefore, this section explains concepts and terminology in the context of the registration of substances under REACH (*i.e.* to help in understanding the full information provided in the REACH Regulation, ECHA Guidance documents and Practical Guides).

2.1. What is grouping of substances?

Substances that are structurally similar with physicochemical, toxicological, ecotoxicological and/or environmental fate properties that are likely to be similar or to follow a regular pattern may be considered as a *group* of substances. These similarities may be due to a number of factors:

- Common functional group (*i.e.* chemical similarity within the group)
- Common precursors and/or likely common breakdown products *via* physical and/or biological processes which result in structurally-similar degrading chemicals
- A constant pattern in the properties across the group (*i.e.* of physico-chemical and/or biological properties)

For registration of a substance under REACH, the information requirements have to be met. Within a group of substances, a data gap might be filled by *read-across*, as described below.

2.2. What is read-across?

The application of the *grouping* concept described above means that REACH information requirements for physicochemical properties, human health effects and/or environmental effects may be predicted from tests conducted on *reference substance(s*) within the group, referred to as *source substance(s)*, by interpolation to other substances in the group, referred to as *target substance(s)*, and this is called *read-across*.

Thus, read-across is regarded as 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)*). Consequently, the read-across approach has to be considered on an endpoint-by-endpoint basis due to the different complexities (*e.g.* key parameters, biological targets) of each endpoint.

The term *analogue approach* is used when read-across is employed within a group of a very limited number of substances for which trends are not apparent: *i.e.* the simplest case is read-across from a single source substance to a target substance.

Alternatively, with a higher number of substances in a group the term *category approach* is used.

Read-across must be, in all cases, justified scientifically and documented thoroughly. There may be several lines of evidence used to justify the read-across, with the aim of strengthening the case.

3. General recommendations applicable to read-across

This chapter lists a series of recommendations applicable to the read-across approach used in a category or in an analogue approach.

3.1. Whenever read-across is used…

Annex XI, section 1.5 of the REACH Regulation requires that whenever read-across is used all of the following conditions should be fulfilled:

a. "*Be adequate for the purpose of classification and labelling and/or risk assessment*" – If the read-across data on the source substance is used as a key study, the data shall be adequate, reliable and robust enough to enable the registrant and the evaluator to decide on the appropriate classification and labelling to apply to the target chemical. Similarly, if the data on the source substance is used as a key study, it shall provide a dose descriptor that is reliable enough to be used for the risk assessment.

b. "*Have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3)*" – Test methods referred

to in Article 13(3) are regularly revised to reflect the progress in science. Due to this process, the revised test methods may include investigations on additional important parameters. The coverage of these key parameters is essential to ensure that the level of information gathered on the source substance is equivalent to that expected from a new study performed according to the most current test method.

c. *"Cover an exposure duration comparable or longer than the corresponding test method referred to in Article 13(3) if exposure is a relevant parameter"* – As an example: a sub-chronic repeated dose toxicity (90-day) study can be used to cover the information requirements for a sub-acute repeated dose toxicity (28-day) study but not vice versa.

d. *"Adequate and reliable documentation of the applied method shall be provided."* – The documentation provided must be sufficient to allow an independent assessment of the adequacy and the scientific validity of the read-across approach. The following elements are considered essential to adequately document a read-across approach:

   i. a read-across hypothesis;
   ii. a justification for the read-across hypothesis;
   iii. a list of all the substances included in the approach;
   iv. detailed substance identity information of all substances included in the approach;
   v. a list of the endpoints that are to be read-across;
   vi. a data matrix;
   vii. a conclusion on the applicability of the proposed read-across approach.

3.2. Make a clear read-across hypothesis and justification

It is essential that the hypothesis for the read-across is clearly presented. The hypothesis should be used to describe the characteristics defining the structural similarities between the source and target substances and any other similarities identified: similarity in breakdown products, or similarities in modes of action.

The read-across hypothesis should also explain why the properties of the target substance can be predicted from the study result(s) of the source substance(s) for each of the endpoints concerned. Therefore, the hypothesis must indicate the endpoint(s) to which the read-across approach applies. If read-across is applied to multiple endpoints, registrants must provide appropriate argumentation (*i.e.* hypothesis and justification) for each endpoint considering the different complexities (*e.g.* key parameters, biological targets) of the individual endpoints.

The read-across justification should demonstrate that the hypothesis is supported based on the available data. The justification should also outline how any shortcomings identified in the approach and the uncertainty associated with the read-across are accounted for.

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

To assess the structural similarity on which the read-across hypothesis is based, unambiguous substance identity information is essential. The absence of adequate information on constituents and/or impurities may undermine the read-across argument.

a. Provide information on substance identity for each substance included in the category or analogue approach. Identifiers such as the CAS No and EC No should be used to identify the substances. Chemical structures of the substances should be provided. Guidance on identification of substances is provided in the ECHA Guidance for identification and naming of substances under REACH.

b. Include the composition and impurity profiles in the substance identity information: this is particularly important for multi-constituent substances and UVCBs. Information on the composition of the substances in the category or analogue approach is relevant when assessing the scientific validity of the approach: minor components and/or impurities may influence the toxicity. This applies for both the category and analogue approach.
c. Include information on the phase or form of the substances. The phase or form of the substances may entail different hazards. It is important to provide evidence that the substances used in the read-across approach are representative for every form and phase covered by the registration dossier and that the read-across does not lead to an underestimation of the hazards of any phases or forms covered by the dossier of the registered substance.

3.4. Outline the structural similarity(ies) between the substances

The structural similarity of the target and the source substances needs to be assessed. The impact of the structural differences between the substances on the endpoint(s) under consideration also needs to be assessed.

The analysis of structural similarity should consider all appropriate elements, notably:

- Presence and number of common functional groups;
- Presence and relevance of non-common functional groups;
- Similarity of the 'core structure' apart from the (non-)common functional groups;
- Potential differences due to reactivity;
- Potential differences due to steric hindrance;
- Presence of structural alerts;
- Position of the double bonds;
- Presence of stereoisomers.

3.5. Toxicokinetics and metabolism

Toxicokinetic information on the substances under consideration, including information on the metabolic fate, can considerably strengthen the robustness of a read-across hypothesis. Any toxicokinetic studies are reported in the format of (robust) study summaries in section 7.1 of the IUCLID dossier. In the absence of such toxicokinetic studies, the absorption, distribution, metabolism and excretion may be assessed based on physicochemical properties and toxicity data.

When the argumentation supporting the read-across is based on similarity through biotransformation processes (metabolic pathway hypothesis), it is essential to demonstrate the existence of this metabolic pathway. In addition, the rate and extent of metabolism of the substances need to be thoroughly investigated and documented to support claims of rapid and complete metabolism. While the notions of rapid and complete metabolism are subjective, the level of information provided shall be sufficient to allow for an independent scientific assessment of the rate and extent of metabolism by the reviewer.

Consideration shall also be given to ensuring that this biotransformation process is the main metabolic pathway for the substances. If alternative metabolic pathways are identified, their impact and relevance, and the (non)-toxicity of the other metabolites shall be assessed. The effect of port of entry/barrier tissues on metabolism and the relevance for humans need to be considered. If appropriate, the conclusions of this assessment should be included in the read-across justification. Toxicokinetic data may contribute to the understanding of the mode of action.

In cases where information on toxicokinetics and metabolism is important for justifying the read-across case, claims should be supported with data. In general, a prediction of the possible

metabolic pathway or a general statement such as "… the substances metabolise through a well-known biological pathway…" is insufficient for supporting read-across.

Guidance on toxicokinetics is provided in the ECHA Guidance on information requirements and chemical safety assessment R.7(c), section R.7.12.

As an example: a registrant claims (*i.e.* hypothesis) that the target substance is rapidly hydrolysed to the source substance following oral administration because the target substance is believed to decompose in the low pH of the stomach. Without supporting data to substantiate the hypothesis, the read-across cannot be accepted. On the other hand, supporting information (*e.g.* experimental studies on hydrolysis at gastric pH, combined with absorption data and PBPK modelling) contributes to increasing the reliability of the read-across approach.

3.6. Physico-chemical properties

A clear understanding of the physico-chemical profile of the source and target substances helps to build a read-across case. Thus, information should be provided for the physico-chemical properties relevant for the toxicological endpoints read-across, *i.e.* molecular weight, Log K_{ow}, water solubility, vapour pressure, granulometry, and dissociation constant.

3.7. Use all available data sources

All data sources shall be considered when developing a read-across approach. Existing data available in the scientific literature or QSAR predictions may constitute useful supporting information to consolidate a read-across hypothesis. However, QSAR predictions alone are normally insufficient to fulfil information requirements for higher tier human health endpoints. Additionally, use of mechanistic data or "*omics*" data can be beneficial in establishing the mode of action. The quality, the reliability and the adequacy of this data should still be critically assessed.

It is not sufficient to quote data obtained from the open scientific literature or to refer to a scientific publication. The relevant data should be reported in the technical dossier in the format of a (robust) study summary to allow for an independent assessment.

QSAR predictions shall be reported in accordance with the reporting formats detailed in the ECHA Guidance on information requirements and chemical safety assessment R.6.

3.8. Substantiate all claims made with supporting data

The documentation of the read-across approach must be adequate for a complete and independent assessment of the approach, both in terms of the underlying data contained within the (robust) study summaries of the source substance(s), and the scientific argumentation justifying the read-across to the target substance(s).

The provision of the underlying data and documentation of the read-across approach is also necessary even if the category or read-across approach has already been used in another regulatory or international context. For example, simply stating that a substance is a member of an OECD category is not by itself a sufficient justification for a read-across.

3.9. Read-across of absence of toxicity is possible

In principle, both positive and negative read-across require the same standard of proof. However, negative read-across may require more information to achieve the same level of certainty as a positive read-across. It should be demonstrated that the absence of toxicity

reported for the source substance does not lead to an underestimation of the toxicity of the target substance. It is essential to demonstrate that the absence of toxicity observed for the source substance is based on robust and reliable scientific evidence in order to make a reliable prediction of the toxicity of the target substance for the endpoint under consideration.

3.10. Read-across and testing proposals

If testing proposals are included in the read-across approach, the information for the proposed source substance(s) are yet to be generated. Therefore, the read-across approach can only be considered at its best as plausible at this stage because the eventual acceptance of the read-across is dependent on the outcome of the proposed tests.

Based on frequently observed shortcomings in testing proposals containing read-across, the following should be included in the justification:

a. A justification as to why the substance(s) proposed for testing is appropriate as the source substance(s) to be read-across to the target substance(s).
b. If the substance to be tested is claimed to be a “worst-case”, this should be justified scientifically.
c. For the proposed substance to be tested, address the composition and impurity profile.
d. If a tiered testing strategy is proposed, indicate the order in which the tests are proposed to be carried out. This includes predefined criteria as to when the testing programme is considered to be concluded and when it will proceed to the next set of proposed tests. Keep in mind that when the testing programme is concluded, the available information should be sufficient for classification and labelling and/or robust risk assessment.

4. Additional recommendations for use of read-across in a category

A category definition presents the criteria for membership of the category, sets the boundaries (applicability domain) of the category and describes all the category members, together with a justification for the choices made in defining the category. In addition, there must be a justification for why read-across is possible within the category (the read-across hypothesis) and a data matrix need to be provided.

4.1. Make a clear category definition

a. The category definition should document the chemical similarities (*e.g.* all category members are linear aliphatic aldehydes) and trends in properties and/or activities that link the category members with each other (*e.g.* the water solubility decreases as the chain length increased). In addition to structural similarity, the category definition may also be based on the mechanism of action or common metabolic pathway.

b. The boundaries (*i.e*. applicability domain) and the structural relationship between the category members have to be known. Clear criteria for category membership should be defined, *i.e.* the grouping should be unambiguous and boundaries of the category clearly specified (*e.g.* category applies to all even-numbered linear aldehydes in the carbon-range from C4-C14… within this there are clear trends for…). There must be a justification for choices made in defining the category, for example, in setting the category boundaries, and inclusion/exclusion criteria for membership of the category.

c. Describe all the category members as comprehensively as possible. Identifiers such as CAS number, IUPAC name and molecular structure contribute the unambiguous identification of the category members and shall therefore be provided. The purity/impurity profile of the substances included in the category should be reported and their impact on the endpoints under consideration should be assessed.

   Consider all substances identified as category members independently of their registration status under REACH.

4.2. Justification for read-across within the category (the read-across hypothesis)

In addition to the issues discussed in section 3.2, the justification should scientifically explain why the read-across is possible. If the category does not contain sufficient, relevant and reliable information to substantiate the hypothesis, it may be necessary to perform or propose further testing to strengthen the justification for read-across.

The justification should also address the structural differences between the substances in order to demonstrate that the differences allowed do not significantly alter the predicted toxicity (*e.g.* the category members differ only in carbon chain length; and as the carbon chain length increases the reactivity of the aldehyde group decreases, as demonstrated by …).

If a substance is part of a category/read-across approach in another regulatory context, the underlying data and category justification still has to comply with the REACH requirements and be in the technical dossier, *e.g.* simply stating that a substance is a member of an OECD category is not by itself a sufficient justification for a read-across.

4.3. Provide a data matrix

A matrix of available data should be constructed with the category members arranged in a suitable order. The ordering of the members should reflect on any trends or progression seen within the category. The cells of the matrix should indicate whether data are available or unavailable. The matrix should also indicate the available reliable key study results.

4.4. Identify and unambiguously present trends in the category

Category members are selected based on the hypothesis that the properties of a group of substances with common structural features will show coherent trends in their physico-chemical properties, in their toxicological (human health/ecotoxicity) effects or environmental fate properties. To use read-across within a category, Annex XI, 1.5 requires properties of a substance to be predicted by means of interpolation.

a. Demonstrate and conclude upon all relevant trends (increasing, decreasing or constant) within your category, ideally both in the data matrix and category justification. Deviations from a trend or inconsistencies in the trend analysis may weaken the category approach and should be justified.
b. As the number of substances being grouped into a category increases, the potential for developing hypotheses for specific endpoints and making generalisations about the trends within the category also increases, and hence the robustness of the category increases.
c. In order to predict a property within a category by means of interpolation, there must be a robust trend, and the target substance must fall within the boundary data points.

A reporting format for categories addressing all of these elements is provided in the Guidance on information requirements and chemical safety assessment chapter R.6.

5. Further information

Further information on how to prepare a grouping of substances and read-across approach can be found in:

- Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.6: QSARs and grouping of chemicals
  http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

- Practical Guide 6: How to report read-across and categories
  http://echa.europa.eu/documents/10162/13655/pg_report_readacross_en.pdf

Adequate documentation of the data used to justify a proposed read-across is crucial for the evaluator when assessing the scientific validity of the read-across approach. Additional useful information can be found in:

- Practical Guide 3: How to report robust study summaries
  http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf

- Guidance for identification and naming of substances under REACH and CLP
  http://echa.europa.eu/documents/10162/13643/substance_id_en.pdf

- Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7(c), Section R.7.12 Guidance on Toxicokinetics
  http://echa.europa.eu/documents/10162/13632/information_requirements_r7c_en.pdf

Information on the Experts Workshop on Read-Across Assessment with active support from Cefic-LRI held at ECHA on 03 October 2012 is available on the ECHA website:

- http://echa.europa.eu/en/view-article/-/journal_content/c6dd5b17-7079-433a-b57f-75da9bcb1de2