

Practical Guide 6

How to report read-across and categories

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| Version | Changes | Date |
|-------------|---|---------------|
| Version 1.0 | First version. | March 2010 |
| Version 2.0 | Revision of the Practical guide addressing structure and content. The update includes the following: <ul style="list-style-type: none"> • Correction of broken hyperlinks throughout the document. • Changes in IUCLID screenshots with associated text improved for more clarity. | December 2012 |
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Practical Guide 6 – How to report read-across and categories

Reference: ECHA-10-B-11.1-EN

ISBN-13: 978-92-9217-094-3

ISSN: 1831-6727

Publ.date: December 2012

Language: EN

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Table of Contents

| | |
|---|-----------|
| 1. Introduction | 5 |
| 2. How to get started with read-across and grouping | 6 |
| 2.1 What is read-across? | 6 |
| 2.2 What is a category (group) of substances? | 6 |
| 2.3 Developing a category hypothesis | 6 |
| 2.4 Substance characterisation | 7 |
| 2.5 Overall assessment of adequacy and reporting | 7 |
| 3. Questions on applying the category concept | 9 |
| 3.1 Which REACH Guidance documents should I read? | 9 |
| 3.2 How do I develop a category? | 9 |
| 3.3 How should I characterise category consistency? | 12 |
| 3.4 How many members should a category have? | 13 |
| 3.5 Is the category estimate adequate for the purpose of classification and labelling and/or risk assessment? | 13 |
| 3.6 When is a category properly documented? | 13 |
| 4. Questions on reporting the category concept | 14 |
| 4.1 How to report a one-to-one read-across using IUCLID 5? | 14 |
| 4.2 How to create a category in IUCLID 5? | 18 |
| 4.3 How to create the registration dossier(s) for a substance that is a member of a category | 22 |
| 4.3.1 Individual submission of the dossier | 22 |
| 4.3.2 Joint submission of the dossiers (lead registrant and members) | 22 |
| 4.3.2.1 Lead registrant tasks | 22 |
| 4.3.2.2 Joint submission members' tasks | 28 |
| 4.4 How do I report a category in the chemical safety report (CSR)? | 29 |
| 5. Further information | 31 |

Table of Figures

| | |
|--|-----------|
| Figure 1: Category section in IUCLID 5 | 19 |
| Figure 2: Category members (substance datasets of all substances used in the category) | 20 |
| Figure 3: Visualisation in the category matrix of the information available in the different substance datasets | 21 |
| Figure 4: Selection in the category matrix of the line related to the endpoint 'solubility in solvent' | 23 |
| Figure 5: Example of a IUCLID 5 Category matrix | 24 |
| Figure 6: Overview of the data available on 'Short-term toxicity to fish' for the different category members | 24 |
| Figure 7: Substance related information | 25 |
| Figure 8: Selection of the categories related to the substance to be registered. | 25 |
| Figure 9: Overview of the information in sections 1 to 3 of IUCLID needed for the category members. | 27 |

| | |
|---|-----------|
| Figure 10: Overview of the components of the dossier..... | 28 |
| Figure 11: Selection of the categories related to the substance to be registered. | 29 |

1. Introduction

The objective of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (hereafter, REACH) are set out in its preamble, including recital 1 which stipulates:

"This Regulation should also promote the development of alternative methods for the assessment of hazards of substances".

In that line, Article 13 of REACH requires that:

"Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across)" (emphasis added).

On this basis, as also described in Annex XI of REACH, a read-across or category approach may be used to fulfil REACH information requirements and, thus, adapt the standard testing regime. This is only possible provided certain criteria are met. If the approach is adequate, unnecessary testing can be avoided. Category and read-across approaches may also be used to define further testing needs in integrated testing strategies to allow efficient targeting of testing. These approaches can also support a conclusion for a REACH endpoint using a Weight of Evidence (WoE) approach. In addition, assessment of a number of chemicals as a category may be more efficient and accurate than assessment of single compounds.

This practical guide provides an overview of important practical aspects on read-across and/or a chemical category approach for substances to be registered under REACH and how to report these in IUCLID 5. However, it does not describe the requirements to pass the technical completeness check or compliance check in dossier evaluation.

2. How to get started with read-across and grouping

2.1 What is read-across?

Read-across is a technique for data-gap filling where endpoint information from one chemical is used to predict the same endpoint for another chemical which is considered to be similar in some important aspect relating to that endpoint, e.g. mode of action, toxicokinetics, metabolism etc. Read-across may be for a qualitative or quantitative result.

Read-across can be performed in the following ways to fill data gaps:

- One-to-one (one analogue used to make an estimation for a single chemical);
- One-to-many (one analogue used to make estimations for two or more chemicals);
- Many-to-one (two or more analogues used to make an estimation for a single chemical);
- Many-to-many (two or more analogues used to make estimations for two or more chemicals).

Same principles apply to both grouping of chemicals (chemical categories) described in this practical guide, and also to read-across. For example, the need to identify the structures and purity profiles of both (or more) substances, the need to justify the read-across in terms of chemical similarity, and the need to document the grouping and read-across information.

2.2 What is a category (group) of substances?

Substances whose physicochemical and/or toxicological and/or 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. These similarities may be due to a number of factors:

- Common functional group;
- Common precursor or breakdown products;
- Constant pattern in changing potency;
- Common constituents or chemical class.

Within a category, a property can be estimated through read-across, trend analysis, and/or (Q)SARs. For a given quantitative category endpoint, the category members are often related by trend.

2.3 Developing a category hypothesis

Practical information on how to form a category is included in section 3.2 'How do I develop a category?' A basis for grouping the chemicals (in terms of their similarity) should be established using the similarity rules specified in Annex XI of the REACH Regulation and further elaborated in Chapter R.6 of the REACH Guidance on information requirements and chemical safety assessment. This could be based on chemical structure, e.g. a common functional group, and/or incremental changes in carbon chain length across the category, or on other common properties such as common precursor and/or breakdown products (metabolites or environmental degradation products), or a constant pattern in the changing potency of the properties across the category. The hypothesis for the derivation of a descriptive group definition should be used to define what characteristics a chemical should have in order to belong to the category (and possibly the exclusion rules). The similarity rules, which could also

be called criteria or principles, might be used individually. However, a category (and similarity) may be justified on more than one basis, for example both a chain length and metabolic pathway category. Multiple justifications usually increase the confidence in the category.

The hypothesis will help identify if the grouping applies to the category members for either environmental or toxicological endpoints or both, and if it is adequate for all routes of exposure and duration of effects.

2.4 Substance characterisation

It is important that the chemical structures and purity profiles of all category members are well defined to establish the category hypothesis, since differences in impurities or stereochemistry can affect the activity and chemical properties. Additionally, the chemical structures of all constituents of the registered substance (including impurities, if relevant) need to be well identified. We recommend following the Guidance on identification and naming of substances under REACH for all category members, not only the substances being registered. UVCB substances should be clearly characterised to every extent possible. It is in the interest of the registrant to describe the substance composition as clearly as possible in order to make optimal use of data.

In IUCLID 5, for each study record documenting data used for a read-across or category approach, the identity of the test substance should be specified if it differs from that defined in section 1 of the REACH dossier. For example, details of chemical name, CAS or EC number for the main components and impurities and the batch number, if available, should be provided.

2.5 Overall assessment of adequacy and reporting

REACH Annex XI foresees the grouping of substances and read-across approach for data gap filling if the following conditions are met:

1. Results are adequate for the purpose of classification and labelling and/or risk assessment;
2. Results have adequate and reliable coverage of the key parameters addressed in the corresponding test methods;
3. An exposure duration comparable to or longer than the corresponding test method is covered, if this parameter is relevant;
4. Adequate and reliable documentation of the applied method is provided.

Grouping approaches can be used to predict the result for a single endpoint or for multiple endpoints, if data are available. In general, read-across approaches which are applicable across several endpoints are more likely to be robust than those which focus only on a single endpoint. The inclusion of long-term as well as short-term endpoints may also increase confidence in the category hypothesis. However, it is important to keep in mind that the robustness of a category depends on the quality and quantity of data available across the members of the category and the degree of similarity (structural, metabolic, mode of action/activity) of the members.

When a registration dossier contains a chemical category or read-across adaptation, it is necessary to include an assessment of the validity of the grouping approach for regulatory purposes. In all cases, a prediction by read-across, (Q)SAR and/or trend analysis could be used as part of a wider WoE approach or as supporting information.

In order to document the validity of the read-across, as part of a category or not, the following options exist:

1. Use the IUCLID 5 category object to report this assessment in the fields under the header 'Justifications and discussions' (see 4.2 how to create a category in IUCLID 5).
2. Without using the IUCLID 5 category object:
 - a) If the validity assessment relates to all endpoints in a category, the Category Reporting Format (R.6.2.6.2 of the Guidance on information requirements and chemical safety assessment) can be attached in section 13; the reporting format for analogues is available in R.6.2.6.1.
 - b) If the justification relates to some endpoints, then the Category Reporting Format validity assessment can be attached (under 'attached background material'), or directly entered at the endpoint study record (in the 'overall remarks' free text area). The same applies to the Analogue Reporting Format if an analogue approach was used.

3. Questions on applying the category concept

3.1 Which REACH Guidance documents should I read?

A summary on how to use non-testing data obtained by applying (Q)SARs and grouping approaches is available in the Guidance on information requirements and chemical safety assessment in chapter R.4.3.2.2 Data obtained by grouping approaches:

[Chapter R.4: Evaluation of available Information](#)

A dedicated section on grouping of chemicals is available the Guidance on information requirements and chemical safety assessment in chapter R.6.2 Guidance on the Grouping of Chemicals:

[Chapter R.6: QSARs and grouping of chemicals](#)

Relevant tools and approaches for the endpoints of interest are offered by each endpoint specific guidance document included in the Guidance on information requirements and chemical safety assessment in:

Chapter R.7: Endpoint specific Guidance ([7a](#), [7b](#), and [7c](#)).

3.2 How do I develop a category?

STEP 1: Check if the chemical is a member of a suitable category that has already been defined.

Some categories have already been described and documented. For example, if you search using a chemical identifier (Chemical Name, EC No, CAS No, etc.) on the ECHA website:

<http://echa.europa.eu>

You will find if a substance has been registered. From the registration dossier you will see if the substance has been registered as a member of a category. If so, then from the category link at the bottom of the disseminated IUCLID dossier you will see which are the other category members listed, for which endpoints the category has been proposed, and any category justification or discussion provided by the registrant.

The categories defined under the OECD HPV program can be found directly from the following OECD website:

<http://webnet.oecd.org/hpv/ui/ChemGroup.aspx>

Alternatively, it could be searched for in the OECD QSAR Toolbox.

It is considered good practice to check for existing categories before the development of new ones. The validity and scope of existing categories should be compared with the REACH information requirements. In addition, when using data from a category for registration purposes, the registrant should be in legitimate possession of, or have permission to refer to, the full study reports in any robust study summaries (REACH Article 10). Existing categories may need to be modified or extended with new members after the collection of additional evidence.

STEP 2: Develop a category hypothesis and definition and identify category members

Define the basis for the category. The category hypothesis should address chemical similarities (analogies) and trends in properties and/or activities that link the category members with each other. Describe the read-across technique (e.g. averaging the results from studies with the analogues, or trend analysis, or any other specific computational methods that have been used to fill the data gap). Lay down the applicability domain for an endpoint in the category. It can be described with inclusion and/or exclusion rules.

For the applicability domain of the category define boundaries for:

- functional groups;
- structural similarities;
- range of values for parameters of interest (e.g. range of Log Kow values which the category members should have);
- for each endpoint, mode or mechanism of action¹ and metabolic similarities supported by toxicokinetic assessment (literature data, *in vitro* data), and comparison of these aspects for each of the category members.

There are a number of software tools available to help in identifying suitable category members such as the OECD QSAR Toolbox. The Toolbox software application (version 3.0) is available for download from:

<http://www.qsartoolbox.org>

together with additional information materials and guidance for installation and use. The software application is developed in a joint effort with the OECD. Version 3 was released at the end of October 2012. It is worth noting that in addition to the support to grouping of substances, the Toolbox could also be used for screening and prioritisation, as well as to facilitate the optimisation of testing strategies within a group of substances.

The OECD Global Portal to Information on Chemical Substances (eChemPortal) is also a useful source of information on chemicals and can be viewed at:

<http://www.echemportal.org>

Another way to identify potential category members/similar substances is to search for pre-SIEF members via REACH-IT. Further guidance on this is available in the REACH-IT Industry User Manual Part 5 – PreSIEF - available at:

<http://echa.europa.eu/web/guest/support/dossier-submission-tools/reach-it/data-submission-industry-user-manuals>

See further information on the methodology in the Guidance R.6.

STEP 3: Gather data for each category member

Get to know the category members. Gather all available data for each category member (including purity and impurity profiles, details on molecular structure of constituents, data on physicochemical properties, environmental fate parameters, toxicological and ecotoxicological effects). The registrant is expected to have legal possession of (or access to) data. Make use of information that is publicly available, literature sources and international assessments related to the category members.

STEP 4: Evaluate available data for adequacy

Evaluate the available data according to the relevant guidance for that endpoint, see Chapter R.7: Endpoint specific Guidance ([7a](#), [7b](#), and [7c](#)).

Does the data meet the REACH information requirements either individually or in a WoE approach? Is the data suitable for classification and labelling and risk assessment?

¹ Mode of action is defined as a series of key biological events leading to an observed toxicological effect. Mechanism of action is a detailed description of the molecular basis of the event (ref. IPCS WHO).

When the underlying experimental data for an endpoint varies (e.g. a mixture of screening and higher tier tests), clarify the scope of the predicted results for the category members with no data. Look for possible trends within the category and breakpoints where there is a change in effect or property. Provide explanations for any observed trend and breakpoints. Data for the registered category members should be comparable to that required by REACH in terms of exposure duration (if relevant) and method. For example, it would not normally be possible to meet the REACH information requirements by read-across of results from an acute, short-term study, to a long-term, chronic endpoint.

STEP 5: Construct a matrix of data availability

A matrix detailing the data available for each endpoint and category member is helpful to describe the category and identify any data gaps. IUCLID 5 can help to build this matrix and can later be used for data gap filling, see Chapter 4.

STEP 6: Perform a preliminary evaluation of the category and fill data gaps

Analyse and verify that the category does in fact exhibit one or more of the trends initially postulated in STEP 2: . Does the category contain sufficient, relevant and reliable information on the category members for assessment purposes? Carry out the assessment for each endpoint, as the category justification might be relevant for some endpoints, routes of exposure or duration of exposure, and not for others.

Data gaps can be filled by read-across, trend analysis and/or application of external (Q)SARs. When using read-across, in general the category approach (with a number of category members contributing data) is preferable to the one-to-one read-across of data from a single analogue chemical since there is generally more confidence in a read-across when it is supported by data from more than one substance. The impact of impurities/differing purity profiles for category members should be considered when applying read-across. The identity of the tested substance should be clear in all cases. For certain toxicological endpoints, a comparison of the target organ effects and the mode of action of the category members need to be taken into account and reported. A WoE approach can be used to increase confidence in data gap filling for any particular endpoint. In general, experimental data is preferred to non-test data for physico-chemical endpoints.

Once the data gaps are filled, check that the REACH information requirements are met for the substances to be registered. The category must be adequate for the regulatory purpose, i.e. the data based on the predicted results has to be adequate for classification and labelling and/or risk assessment and PBT assessment (see REACH Annex XI).

STEP 7: Propose and perform testing if necessary

If there is insufficient data to assess all category members, it may be necessary to perform or propose testing. Generate a category test plan which identifies key substances for testing; this could also include toxicokinetic data or *in vitro* data to support the category hypothesis.

Testing for Annex IX and X endpoints requires submission of a testing proposal to ECHA - See Guidance on Registration

http://echa.europa.eu/documents/10162/13632/registration_en.pdf

STEP 8: Revise the assessment of the category

If new data is generated, this should be evaluated and the category reassessed to determine whether the original hypothesis and definition made in STEP 2: (Develop a category hypothesis and definition and identify category members) are correct. If the results support the category, the data-gap filling can be completed. If the results do not support the category, further testing may be required; the category may need to be re-defined.

STEP 9: Report and document the final category

It is important to provide adequate and documented justification of the category approach in the IUCLID 5 dossier, including a detailed justification to explain how the REACH Annex XI criteria (similarity rules) for categories (grouping of substances) are addressed. Every category member subject to registration should meet the REACH information requirements for their particular tonnage, whether using predicted or experimental data.

Sufficient details should be provided for the available studies to allow a rational evaluation of the category. Robust study summaries should be provided where possible. However, when using data from a category member for registration purposes, the registrant shall be in legitimate possession of or have permission to refer to the full study reports summarised in any study summaries or robust study summaries (REACH Article 10). Where insufficient experimental details are available, consider documenting the information as a supporting study. Further guidance, on how to document and report categories in IUCLID 5, is available in Chapter 4 of this document.

3.3 How should I characterise category consistency?

A category is consistent when all category members have functional groups that allow the expectation of a similar mode/mechanism of action, similar toxicokinetic behaviour and/or similar likelihood of breakdown products (i.e. absence of outlying effects for all applicable endpoints) for the endpoints under consideration. A category is also consistent if a constant pattern is observed in a changing potency of the properties across the category.

Consideration should be given to apparent outliers in a category, i.e. those substances with outlying behaviour which do not appear to follow the same trend as other members for a given endpoint. Justification for including or excluding category members which demonstrate outlying behaviour for specific endpoints should be provided in the IUCLID 5 dossier. The assessment of outlying behaviour could be strengthened by other available data, such as *in vitro* results, (Q)SAR predictions or results for other endpoints.

The following issues could be considered when assessing the consistency of a category:

- **Empirical (structural) similarity**
 - chemical functionalities
 - statistical similarity above a user defined threshold
- **Mechanistic similarity**
 - interaction mechanisms
 - mode of action
 - reactivity profiles
- **Similar bioavailability and metabolic profile**
- **Toxicological effect (for complex chronic endpoint)**

The OECD QSAR Toolbox can be used to evaluate the category consistency using a number of profilers (IT-coded knowledge, usually in a form of decision tree). The substance can be grouped according to category (e.g. US EPA, OECD categories), empirical (e.g. functional groups), endpoint-specific (e.g. *in vitro* mutagenicity) or mechanistic profilers (e.g. DNA binding protein binding). The Toolbox also offers a convenient tool for screening, and possibly prioritisation.

3.4 How many members should a category have?

Ideally, the category should have as many similar substances as available, from the beginning when the category is hypothesised. This will allow complete analysis of data availability and data gaps for all these members, as well as trends and outliers, for selected endpoints. If data gaps have to be filled with test data, an objective choice of members to be tested would be possible (rational test design). For practical reasons, however, it is not always possible to gather all category members together, and the lack of data often hampers the interpolation of data between the members. Therefore, the simplest category could be of two members, which equals a one-to-one read-across, and there is no upper limit for the number of members to be included. However, when more substances participate in a category, there is a need for a strong hypothesis, detailed applicability domain description, and robust justification. The category justification is stronger when more analogues are gathered, there are enough bridging data to indicate that the category members are similar enough/show a consistent pattern, and this is demonstrated evidently by the registrant.

3.5 Is the category estimate adequate for the purpose of classification and labelling and/or risk assessment?

To be adequate, a category prediction should be adequate for the purpose of classification and labelling and/or risk assessment. The adequacy of the category prediction for the purpose of classification and labelling and/or risk assessment will be very much endpoint-dependent. Additional information might be needed to assess the generated prediction for adequacy in the context of a regulatory decision. Therefore, the validity, applicability and relevance can only be considered on a case-by-case basis.

3.6 When is a category properly documented?

A category should include satisfactory substance identification of all its members, including constituents, and purity/impurity profiles. The documentation should also contain a detailed description of the hypothesis for the grouping and read-across, including toxicokinetic considerations when used for toxicological endpoints. The category justification should include comparison of experimental data for the category members and a clear data matrix, highlighting any trends within data. Although it is important to document a category well to allow appropriate evaluation by an assessor, a well documented category does not automatically mean that it is robust. The robustness of a category or read-across from an analogue will depend on the validity of the hypothesis and its scientific basis, as well as on the presented evidence.

4. Questions on reporting the category concept

4.1 How to report a one-to-one read-across using IUCLID 5?

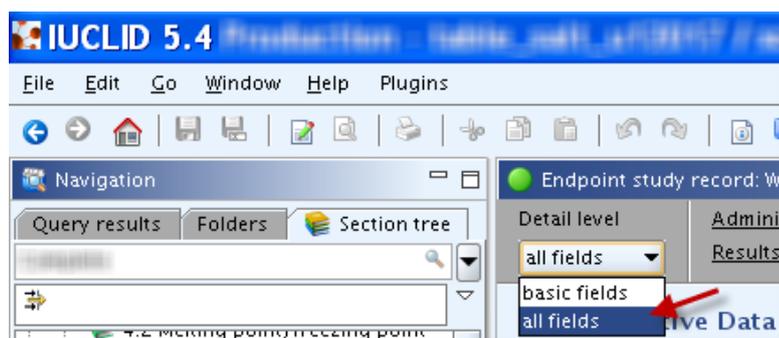
Physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substances within a group, when the substances are likely to be similar or follow a regular pattern as a result of such similarities.

Within a category, the category members are often related by trend. When the grouping is based on a very limited number of chemicals and trends are not apparent, the term “analogue approach” is used. The simplest form of analogue approach (as of category approach) is one-to-one read-across.

See the Guidance on information requirements and chemical safety assessment, Chapter R.6: (Q)SARs and grouping of chemicals; Chapter R.6.2.6.1 gives more details on reporting of analogue approach while chapter R.6.2.6.2 gives more details on the reporting format for a chemical category.

The information shall be reported in the IUCLID 5 endpoint study record as follows:

Select “all fields” in the “Detail level” dropdown menu.



Block “Administrative data”

- The field “Purpose flag” to state whether the estimate is used as a key study, a WoE approach, or as supporting study.
- The field “Study result type” to state “read-across from supporting substance (structural analogue or surrogate).”

Endpoint study record: Short-term toxicity to fish.001

Detail level: **all fields** ▼

Administrative Data Data source Materials and methods
Results and discussions Overall remarks, attachments Applicant's summary and conclusion

Administrative Data



Purpose flag: key study  ▼ robust study summ

Data waiving:  ▼

Justification for data waiving:

Study result type: read-across from supporting substar  ▼  ▼ Study period:

Set the reliability as necessary and enter the hypothesis for the analogue approach in the "Rationale for reliability incl. deficiencies" field, as indicated below. Select a suitable reliability score but bear in mind that the maximum for read-across is 2.

Reliability: 2 (reliable with restrictions)  ▼

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

Block "Test materials"

- Select "no" in the drop down menu "Test material same as for substance defined in section 1 (if not read across)".
- In the field "Test material identity" include information on the source substance.
- The field "Details on test material" to include the structural representation (e.g. SMILES notation) and possible descriptor values if used and as used to derive the prediction. Please note that the IUCLID 5 free text template gives the possibility to already pre-fill the structure of the information to be inserted in this box.
- Confidential information can be placed in "Confidential details on test material".

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

Provide details on properties of the source substance in the "Details on properties of test surrogate or analogue material" (if available). Confidential information can be placed in "Confidential details on test material". The IUCLID 5 free text template gives the possibility to already pre-fill the structure of the information to be inserted in this box. Please note that this field (details on properties of test surrogate or analogue material) is not available in all endpoint IUCLID sections and should only be filled for endpoints, where it appears available.

Details on properties of test surrogate or analogue material

PHYSICO-CHEMICAL PROPERTIES

- Melting point:
- Boiling point:
- Vapour pressure:
- Water solubility (under test conditions):
- Henry's law constant:
- log Pow:
- pKa:
- Stability in water:
- Stability in light:
- pH dependance on stability:

OTHER PROPERTIES (if relevant for this endpoint)

- Results of test for ready biodegradability:
- Other:

Block "Results and discussions"

- In a standard case you are requested to provide results in the foreseen 'Effect concentrations' repeatable block fields. It will allow you to automatically transfer

information from these result fields to the CSR when the IUCLID 5 CSR plugin is used. The list of fields to be filled in the "Results and discussions" block will vary depending on the endpoint. Therefore, we recommend consulting the Data Submission Manual 5 "How to complete a technical dossier for registrations and PPORD notifications" available in the ECHA website at:
<http://echa.europa.eu/web/guest/support/dossier-submission-tools/reach-it/data-submission-industry-user-manuals>

for instructions on how to fill the results.

The field "Any other information on results incl. tables" shall include the description of the analogue approach justification based on available experimental data, including basic physico-chemical properties, summarise how these results verify that the read-across is justified. The data should also show that functional groups not common to source and target chemicals do not affect the anticipated toxicity (data matrix can also be entered in this field "Any other information on results, incl. tables"). The available experimental results reported in the data matrix should support the justification for the read-across.

It is advised to additionally create an endpoint summary when more than one endpoint study record is available and provide the justification on read-across/category in the "Discussion" field of the endpoint summary together with the overall assessment on the particular endpoint. This will enable the automatic transfer of this information to the CSR when the IUCLID 5 CSR plugin is used. If there is only one endpoint study record provided on read-across, you may still copy-paste the justification from the endpoint study record to the "Discussion" field in the endpoint summary for the above stated reasons.

Results and discussions

Effect concentrations

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

Add... Edit... Delete

Any other information on results incl. tables

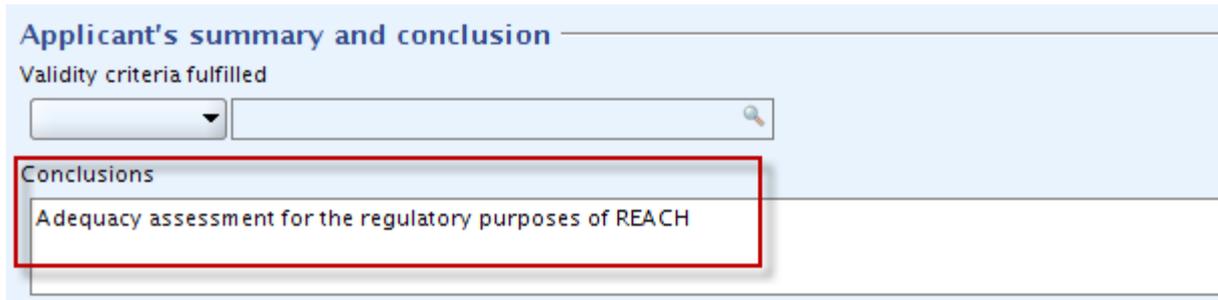
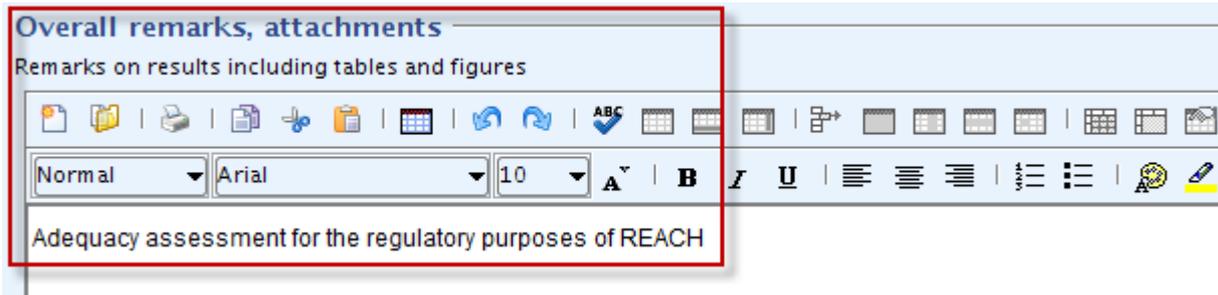
Normal Arial 10 A B I U

Enter the analogue approach justification.

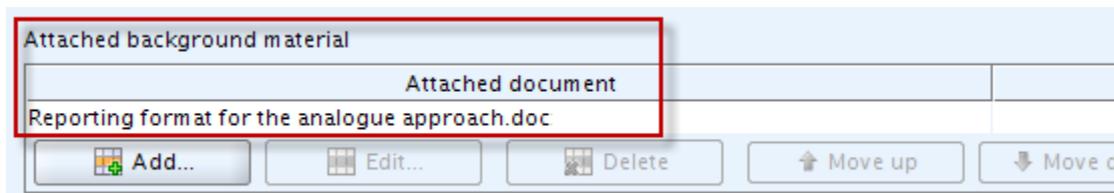
Enter the data matrix with the available experimental results.

Block "Overall remarks, attachments" and/or "Applicant's summary and conclusions"

- The result of the adequacy assessment for a regulatory purpose (risk assessment, classification & labelling, PBT analysis) should be reported in "Overall remarks", "Conclusion" and/or "Executive summary".



Any supporting documents (e.g. a PDF of already composed reporting form for analogue approach) should be attached in the "Attached background material" field.



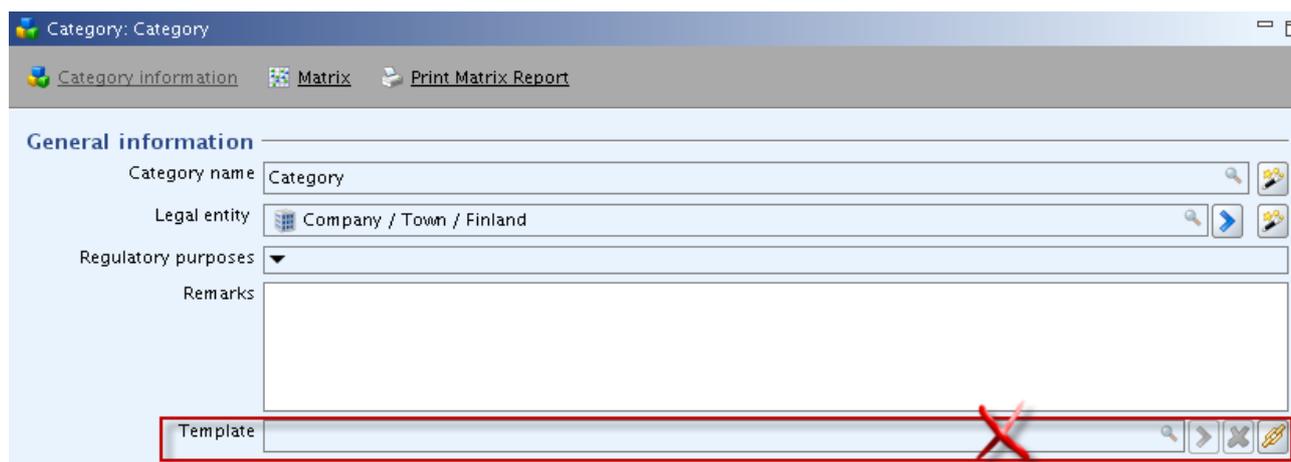
4.2 How to create a category in IUCLID 5?

IUCLID 5 allows the creation of a category for *substance REACH registration dossier* for a substance belonging to a category of substances as defined under REACH Annex XI 1.5.

IUCLID 5 was designed to grant the necessary flexibility to fulfil different regulatory requirements. In some programs (e.g. OECD HPVC) only one dossier might be created for the whole chemical category, including all category members. The REACH Regulation, however, requires the creation of a separate dossier for each substance (category member or otherwise) to be registered. As a result of this requirement under REACH, if a registrant wants to register two substances with read-across arguments, these arguments should be included independently (and repeatedly) in both dossiers. For all information needed on how to proceed when creating a dossier, please check the IUCLID 5 end user manual (D.6.2.1. Creating and populating substance datasets for all category members).

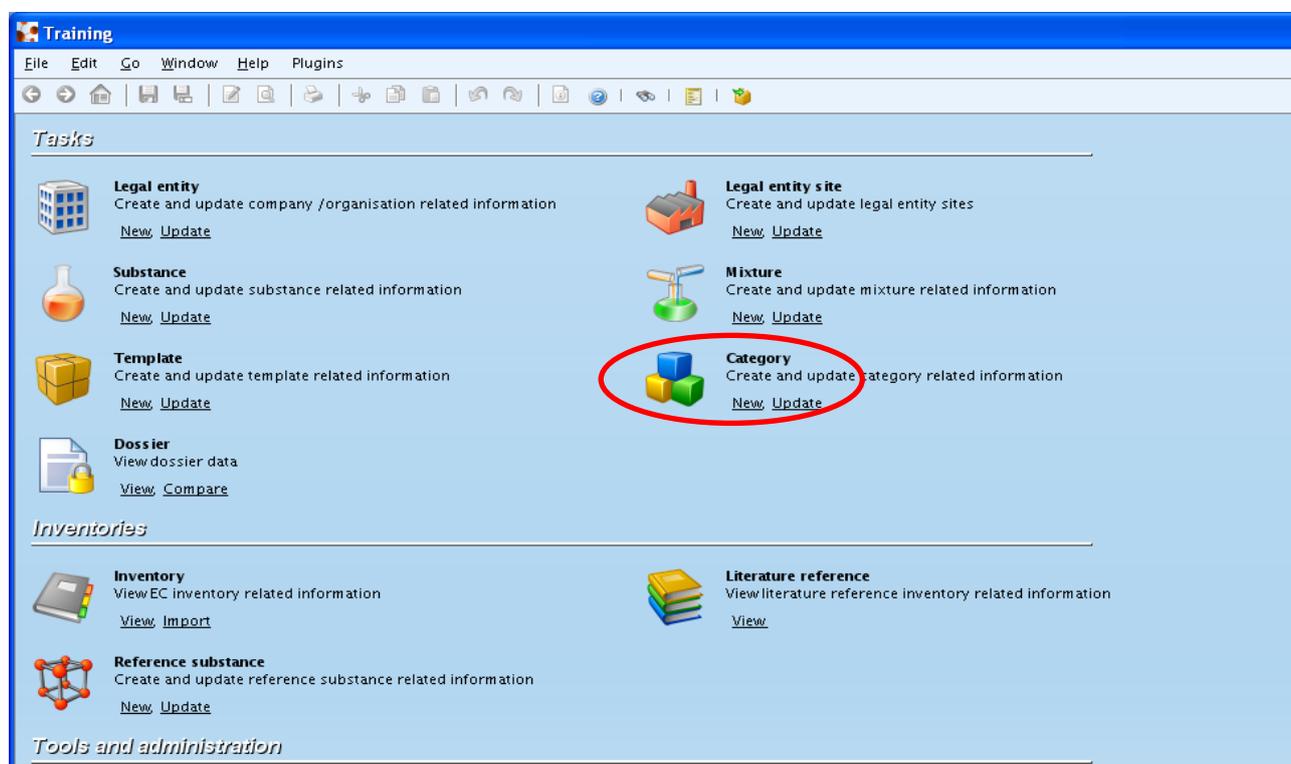
The different steps to follow for creating a category in IUCLID 5 are detailed here below.

Note: It is recommended to avoid attaching a IUCLID 5 template in the IUCLID 5 category object (see screenshot below) since the use of a template in the category will lead to an incorrect visualisation of the matrix with all information available in the different substance datasets.



- Go to the category section in IUCLID 5

Figure 1: Category section in IUCLID 5



- In order to create a category, choose 'New'. Specify the name of the category in the popup window that opens.
- In the 'category members' repeatable block section, link the substance dataset of the substance you want to register under REACH as well as all other substance datasets to be used in the category. To add a new substance dataset to the category, use the green '+' button. Please note that, as specified above, the substance datasets of all category members should contain information in sections 1.1, 1.2 and all endpoint information.

Figure 2: Category members (substance datasets of all substances used in the category)

The screenshot shows a web application window titled "Category: gluconates CECD". The interface is divided into two main sections: "General information" and "Category members".

General information section:

- Category name:** gluconates CECD
- Legal entity:** EUROPEAN COMMISSION - European Chemicals Bureau / vv / Italy
- Regulatory purposes:** (dropdown menu)
- Remarks:** (text area)
- Template:** (text field)

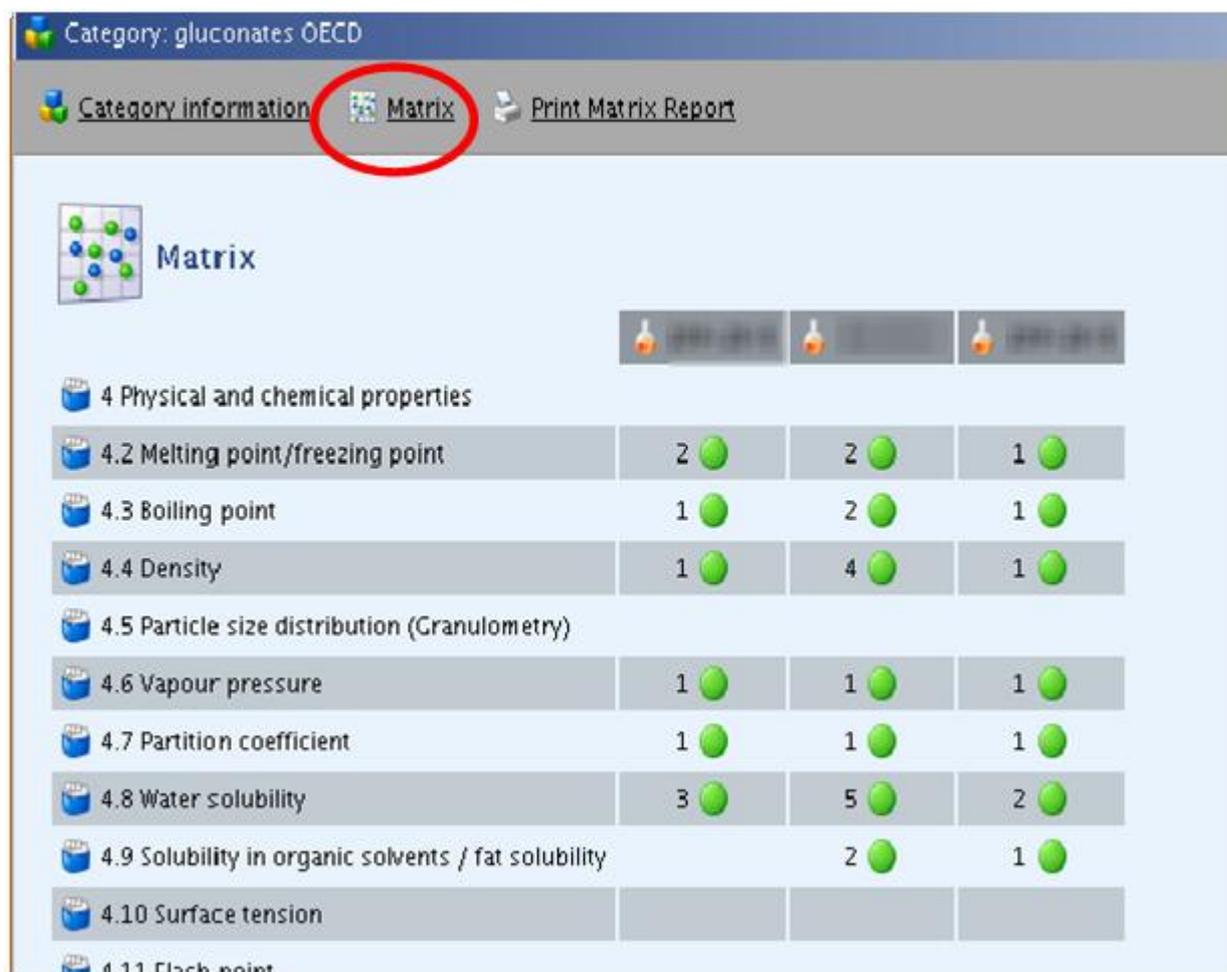
Category members section:

This section displays a list of substance datasets, each with a set of icons for actions (select, delete, etc.). The following table summarizes the data shown:

| Substance Dataset | Actions |
|--|----------------------------------|
| 299-27-4 / potassium gluconate (UC4 DSN 101) | Select, Delete, Add, Edit, Print |
| 526-95-4 / D-gluconic acid (UC4 DSN 103) | Select, Delete, Add, Edit, Print |
| 299-25-8 / calcium gluconate (UC4 DSN 102) | Select, Delete, Add, Edit, Print |

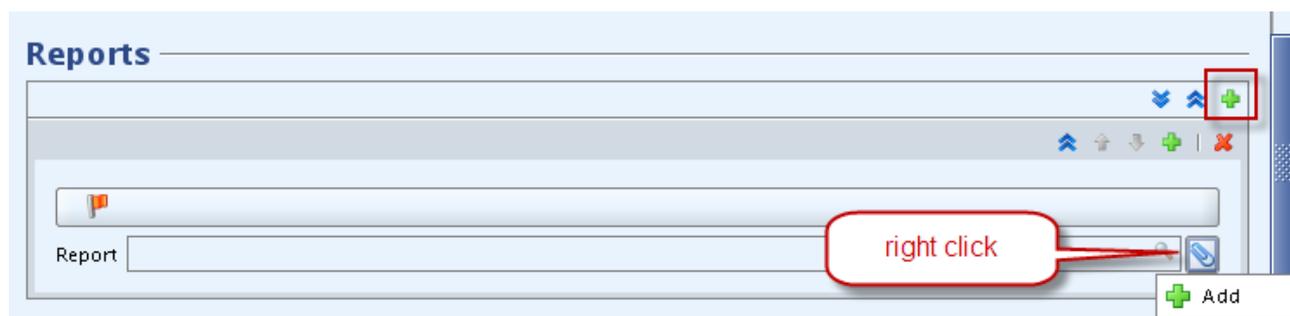
- In the "Category endpoint" section, select the endpoints for which you would like to apply the category to. One or several endpoints can be selected. If all endpoints are considered relevant, click the "select all" button. Please remember that only the endpoints indicated in this section will be displayed in the matrix.
- Add the justification of the category – see section R.6.2 in: [Guidance on Information requirements and Chemical Safety Assessment](#)
- The category matrix displays all endpoints listed in the different substance datasets (Figure 3).

Figure 3: Visualisation in the category matrix of the information available in the different substance datasets



Important note: if you want to attach more than one category to your substance dataset for specific properties, you will have to create as many categories as needed. For example, if you need to define some "category members" for the ecotoxicological properties, and some different "category members" for the toxicological properties, then, you will have to define two different categories, specifying for each of them the related substance datasets, as well as the necessary endpoints.

The Reporting Format for the analogue approach (Chapter R.6: (Q)SARs and grouping of chemicals - R.6.2.6.1), the reporting format for a chemical category (Chapter R.6.2.6.2) as well as all other supporting documents, can be attached as a stand alone document under the header "Report" in the category information page. Several documents can be attached by clicking the green "plus" button as indicated in the following screenshot. Otherwise, the fields under 'Justifications and discussions' should be completed (e.g. Category definition, Category rationale).



4.3 How to create the registration dossier(s) for a substance that is a member of a category

The aim of these instructions is to explain how to prepare a registration dossier for a substance which is part of a category of substances (as defined under REACH Annex XI, section 1.5) using IUCLID 5.

4.3.1 Individual submission of the dossier

Before sending an individual submission for a substance in a category, registrants should ensure first that they are fulfilling the data sharing obligations for that substance. If there are no other registrants for the substance to be registered, then a joint submission is not necessary, and the dossier including the category should be prepared in the same way indicated below for lead registrants (4.3.2.1).

Since it is necessary to submit one registration dossier per substance, registrants who manufacture/import several substances that are part of a category may need to submit individually for some members of the category (for which they are the only manufacturer/importer) and jointly for others (for which there is more than one registrant, see 4.3.2).

4.3.2 Joint submission of the dossiers (lead registrant and members)

To correctly proceed with the preparation of the joint submission dossier for a substance belonging to a category in IUCLID 5, some steps should have been performed already. The guidance below assumes that the substance datasets of the different category members are already filled and ready to use (for more information refer to the IUCLID 5 user manual chapter D.4. Substance (Create and update substance related information)).

Note: to correctly submit a joint submission dossier, the lead registrant has to submit the dossier to ECHA before the member(s).

4.3.2.1 Lead registrant tasks

When preparing a dossier on a substance that is member of a category in IUCLID 5, the lead registrant should:

- Develop datasets of all the substances used in the category with all relevant Endpoint Study Record (ESRs);
- Determine reference substances (reporting the substance identification) of all the substances used in the category (each dataset should refer to a Reference substance);
- Provide its legal entity (LEO);

- Develop a IUCLID 5 category (in which all the substances identified previously, and for which there is a dataset, are considered as 'category members').

The lead registrant of the substance should follow the subsequent steps:

Ensure that the substance dataset for the substance to be registered is complete according to REACH requirements for the tonnage band related to their registration. This is to ensure that the substance passes the technical completeness check; please refer to "DSM 5: How to complete a Technical Dossier for Registrations and PPORD Notification" available on ECHA website:

<http://echa.europa.eu/web/guest/support/dossier-submission-tools/reach-it/data-submission-industry-user-manuals>

For the different endpoints, where there is a data gap and where a read-across to another substance of the category is intended to be used, the user can follow the following steps:

- Go to the category matrix and select the line concerning the relevant endpoint (e.g. solubility in organic solvent).

Figure 4: Selection in the category matrix of the line related to the endpoint 'solubility in solvent'

| Endpoint | Substance 1 | Substance 2 | Substance 3 |
|---|-------------|-------------|-------------|
| 4 Physical and chemical properties | | | |
| 4.2 Melting point/freezing point | 2 | 2 | 1 |
| 4.3 Boiling point | 1 | 2 | 1 |
| 4.4 Density | 1 | 4 | 1 |
| 4.5 Particle size distribution (Granulometry) | | | |
| 4.6 Vapour pressure | 1 | 1 | 1 |
| 4.7 Partition coefficient | 1 | 1 | 1 |
| 4.8 Water solubility | 3 | 5 | 2 |
| 4.9 Solubility in organic solvents / fat solubility | | 2 | 1 |
| 4.10 Surface tension | | | |
| 4.11 Flash point | | | |
| 4.12 Auto flammability | 1 | | |

- Fill the data gap using read-across with the relevant information coming from other category members.

We recommend using the copy and pasting functionality to enter the full endpoint study record of the analogue into the substance dataset and modify it as follows:

- Select "read-across based on grouping of substances (category approach)" in the 'Administrative data' section from the "Study result type" pick list;
- Adjust reliability as appropriate;

- Specify that the test material is not the same as for the substance defined in section 1: select "no" in the drop down menu "Test material same as for substance defined in section 1 (if not read across)" and indicate the substance identifiers in the "Test material identity". Further details on the substance identification can be given in "Details on test material" or "Confidential details on test material".

Figure 5: Example of a IUCLID 5 Category matrix

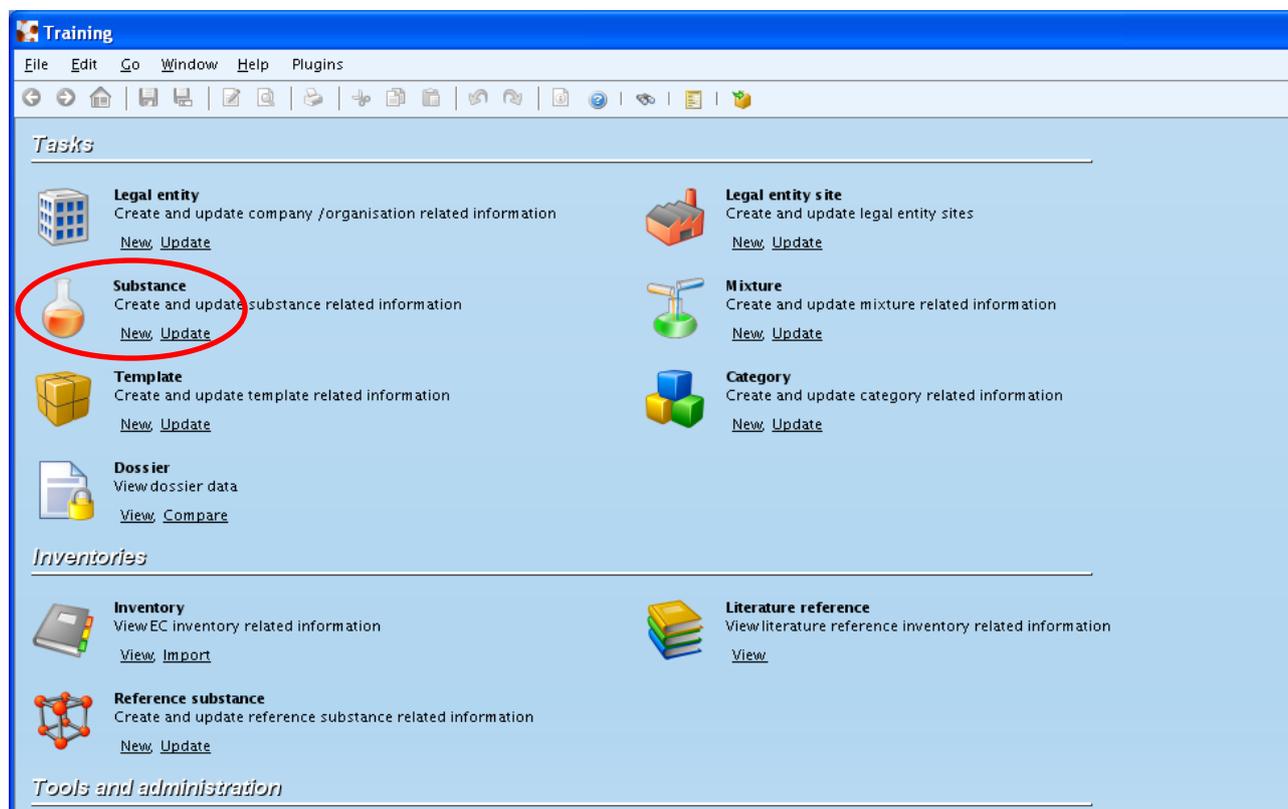
| | 97-43-2 | 97-43-2 | 97-43-2 | 687-43-2 |
|--|---------|---------|---------|----------|
| 4.2 Melting point/freezing point | 1 | 1 | 1 | 1 |
| 4.3 Boiling point | 1 | 1 | 1 | 1 |
| 4.4 Density | 1 | 1 | 1 | 1 |
| 4.6 Vapour pressure | 1 | 1 | 1 | 1 |
| 4.7 Partition coefficient | 1 | 1 | 1 | 1 |
| 4.8 Water solubility | 1 | 1 | 1 | 1 |
| 5.1.2 Hydrolysis | 1 | | 1 | 1 |
| 5.2.1 Biodegradation in water: screening tests | 1 | 1 | 1 | 1 |
| 5.3.1 Bioaccumulation: aquatic / sediment | | | | 1 |
| 6.1.1 Short-term toxicity to fish | 1 | 1 | 1 | 1 |

By clicking the line referring to '6.1.1 Short-term toxicity to fish' an overview of the information available on this endpoint is displayed as presented in Figure 6.

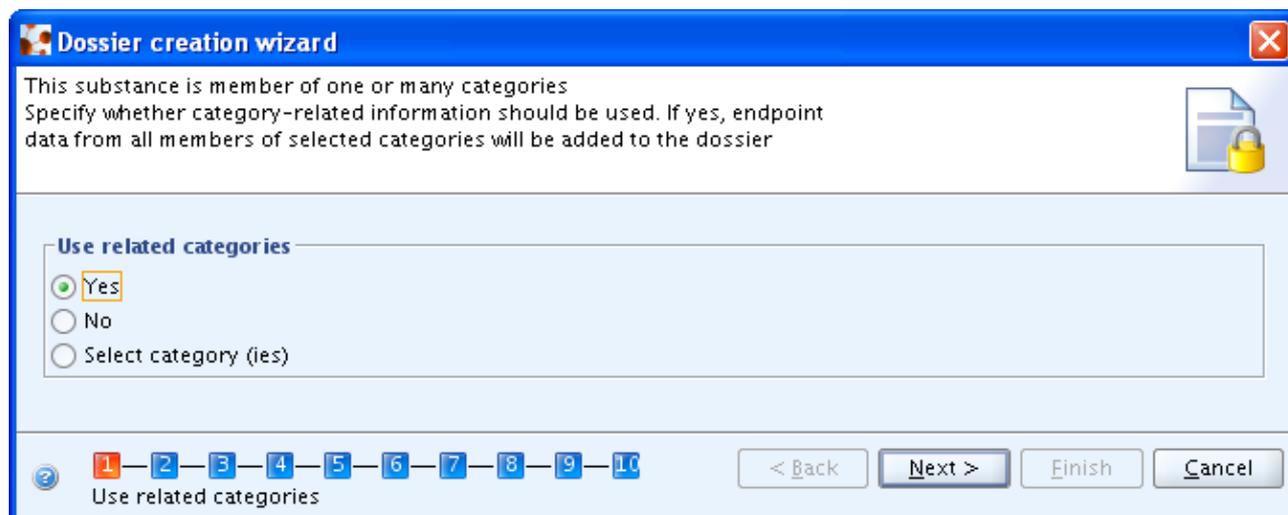
Figure 6: Overview of the data available on 'Short-term toxicity to fish' for the different category members.

| Category Member | Short-term toxicity to fish.001 |
|---|---------------------------------|
| Ethyl Methacrylate (EMA) / ethyl methacrylate / ethyl methacrylate / 97-63-2 / rbbi_company | Short-term toxicity to fish.001 |
| Iso-Butyl Methacrylate (i-BMA) / isobutyl methacrylate / isobutyl methacrylate / 97-86-9 / rbbi_company | Short-term toxicity to fish.001 |
| n-Butyl Methacrylate (n-BMA) / butyl methacrylate / butyl methacrylate / 97-88-1 / rbbi_company // national // France | Short-term toxicity to fish.001 |
| 2-Ethylhexyl Methacrylate (2-EHMA) / 2-ethylhexyl methacrylate / 2-ethylhexyl methacrylate / 688-84-6 / rbbi_company | Short-term toxicity to fish.001 |

- Go to Home|Substance and select the substance dataset to be registered in REACH (Figure 7).

Figure 7: Substance related information

- From this substance dataset, create the dossier following the wizard steps (Figure 8) (only the steps relevant for the creation of a dossier for a substance belonging to a category are listed here below. For more information the Guidance on IUCLID should be consulted).
- Select the checkbox "Yes" under "Use related categories" popup window.

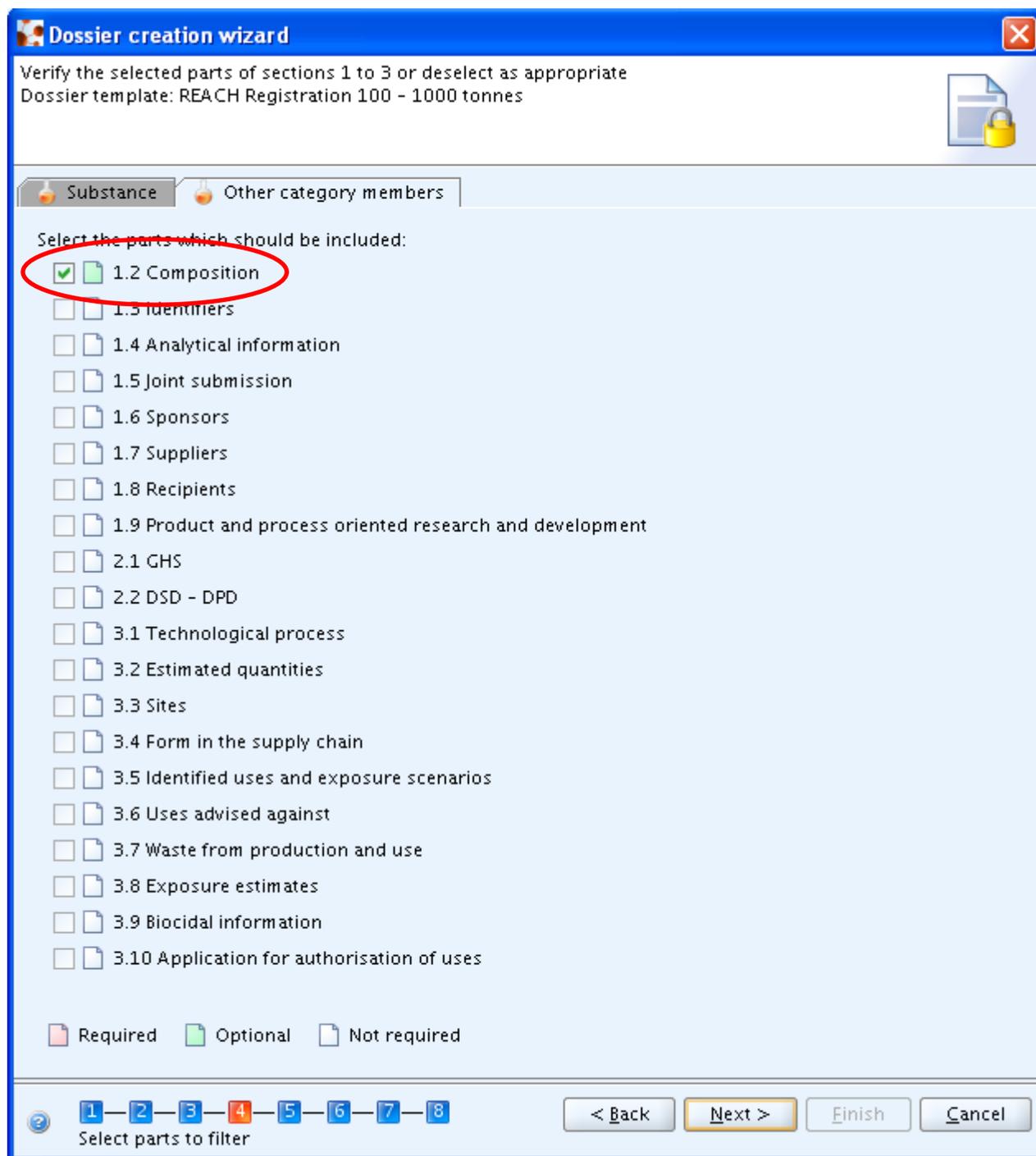
Figure 8: Selection of the categories related to the substance to be registered.

Note: If the substance to be registered belongs to more than one category, the registrant should tick the

box "select category (ies)" and select the correct category or categories that will be displayed.

In the dossier creation wizard, for IUCLID sections 1 to 3, by default only section '1.2 Composition' is ticked in 'Other category members' tab (Figure 9). This default setting should be kept as only the information related to the substance composition is needed in the lead registration dossier in order to assess the validity of the category. Please note that all other information related to the category members (e.g. information on manufacture, use and exposure) is not relevant for the lead registration dossier, as it should be provided by each of the co-registrants in their registration dossier.

Figure 9: Overview of the information in sections 1 to 3 of IUCLID needed for the category members.



- Select the dossier template that covers the highest tonnage band of the joint submission. Complete all the steps to complete the dossier creation.

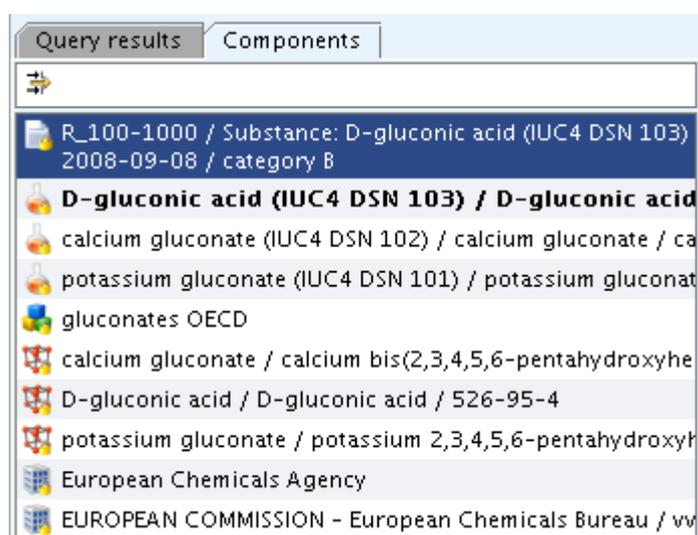
For more information on how to correctly create a dossier, please refer to the Data Submission Manual 4: 'How to Pass Business Rule Verification ("Enforce Rules")' available on the ECHA website at:

<http://echa.europa.eu/web/guest/support/dossier-submission-tools/reach-it/data-submission-industry-user-manuals>

Once the dossier is created, it will contain the following information (Figure 10):

- Dossier header;
- The information on the:
 - substance to be registered by the lead registrant (displayed in bold): for this substance all the sections required by the REACH Regulation have to be filled in;
 - The other substances used as category members: the only information displayed in the registration dossier for those substances is related to sections 1.1 and 1.2;
- The reference substances related to the substance to be registered as well as all the substances used as category members;
- The category containing the links to the category members, in which all the endpoints that were defined in the “category” object, are available for all category members;
- The legal entity object (LEO) of the lead registrant.

Figure 10: Overview of the components of the dossier.



For more details on joint submissions, please refer to the “Industry User Manual part 7 joint submission” available on the ECHA website:
<http://echa.europa.eu/web/guest/support/dossier-submission-tools/reach-it/data-submission-industry-user-manuals>

4.3.2.2 Joint submission members’ tasks

The members of the joint submission have to submit a ‘joint submission member registration dossier’ and select in the dossier header their own tonnage band of the substance they produce and/or import.

Except when the member opts out for one of the information specified in Article 11 of the REACH Regulation, the only information included in the individual IUCLID registration dossier, should be the information in sections 1 and 3 and a reference to the joint submission and other members in section 1.5.

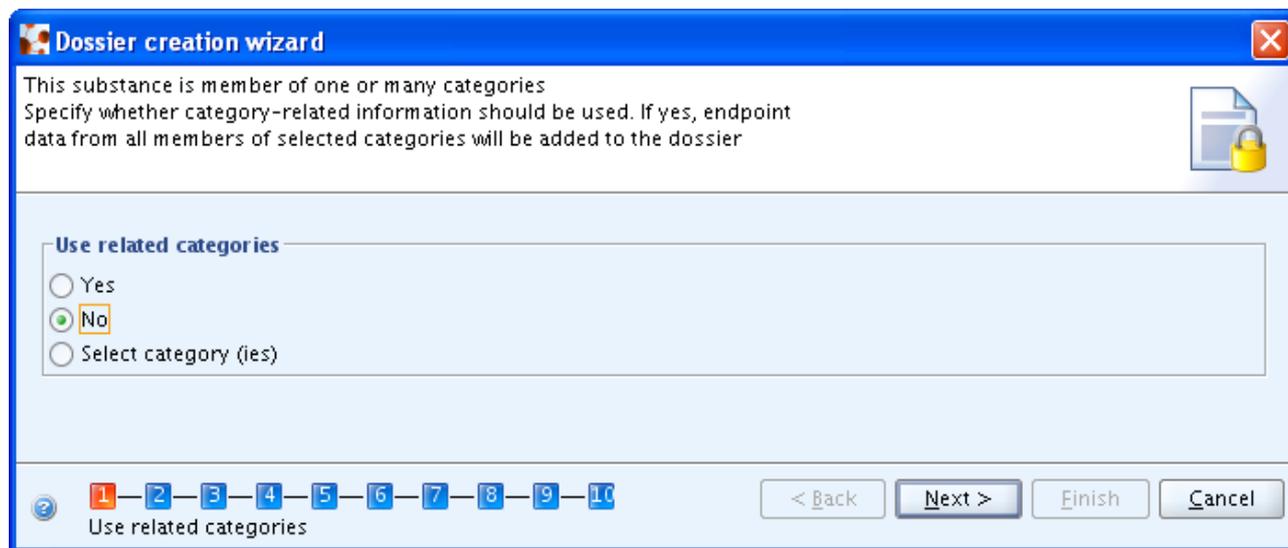
The registration dossier will then contain:

- Dossier header;
- Substance dataset for the substance to be registered where sections 1 and 3 have to be filled;
- The reference substance related to the substance to be registered;

- The legal entity object of the joint submission member.

The steps to follow in order to create the dossier are the same as for the lead registrant. However, the members of a joint submission do not have to select the category, as only the lead registrant sends a full dossier. Therefore, for members, in the dossier creation wizard the "No" checkbox should be selected (Figure 11).

Figure 11: Selection of the categories related to the substance to be registered.



4.4 How do I report a category in the chemical safety report (CSR)?

A reporting format for reporting categories in the CSR is not yet available. Therefore, the reporting format available for single substances (Guidance on information requirements and chemical safety assessment, Part F) has to be adapted in a way that all the necessary information on the category can be included in the CSR.

The category hypothesis and justification including information on which endpoints, routes of exposure and relevant types of effects are covered by the category shall be presented under the hazard assessment in the CSR (sections 4-8) for both human health and environmental assessment where the category is relevant. The justification shall also include how the similarity rules specified in Annex XI of REACH are met and if there are any sub-categories within the main category. This needs to be done manually by adding the text in the CSR (preferably at the introduction of each hazard assessment e.g. section 5 Human Health Hazard Assessment, section 7 Environmental Hazard Assessment). This applies when one uses either the IUCLID 5 CSR plugin or creates the CSR without the IUCLID 5 CSR plugin tool.

It is also advisable to include the IUCLID 5 data matrix in case the category has been built using the IUCLID 5 category function. This can be easily done by copying and pasting the printout of the matrix built in IUCLID. The data matrix before the filling of the data gap should be illustrated. To do so, the user should first go to the interested category matrix report, press print and from the browser that opens, copy the matrix data and paste them into the CSR below the category hypothesis and justification. In this way, the data that is included in the matrix is also pasted in the CSR.

Moreover it is advisable to include, in tabular format under section 3 of the CSR, the classification and labelling of all the substances that are members of the category to allow comparison of their hazard properties. In addition, tables under each endpoint (physicochemical, (eco)toxicological, environmental fate) listing the hazard summary for each

of the members of the category, with an indication of which members have measured data for an endpoint, is extremely useful as it allows proper evaluation of the category justification and robustness of the prediction of hazard for those members of the category where read across is used (if the IUCLID 5 category function has been chosen, all data is available in the matrix report).

5. Further information

- Guidance on information requirements and chemical safety assessment
<http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>
- (Q)SAR Application Toolbox
<http://www.oecd.org/chemicalsafety/testingofchemicals/oecdquantitativestructure-activityrelationshipsprojectqsars.htm>
- OECD categories by OECD
<http://webnet.oecd.org/hpv/ui/ChemGroup.aspx>
- OECD Global Portal (eChemPortal)
http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en
- Data Submission Manual 5 'How to complete a technical dossier for registrations and PPORD notifications'
http://echa.europa.eu/documents/10162/13653/dsm5_tech_dossier_en.pdf
- IUCLID 5 end-user manual
<http://iuclid.echa.europa.eu/index.php?fuseaction=home.documentation&type=public>

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