General tips on how to bring your registration dossier in compliance with REACH

27 September 2012 / Benoit Dilhac

Overview

1) Substance identification
2) Endpoints
   - Robust study summaries
   - Read-across
   - QSARs
   - Weight of evidence
3) Chemical safety assessment

Substance identification

1) Identification of the 'real' substance manufactured or imported

Each registrant, and especially members, must submit their own substance identity information:

- Own identified impurities and additives.
- Own concentration ranges of constituents, impurities and additives.
- Own analytical data (IR, NMR, UV spectra and GC or HPLC)
  - If these techniques are not suitable for your substance, please provide data from another characterization method (e.g inorganic substances: XRD and elemental analysis).

2) Proper identification of UVCB

UVCB must be described by:

- Their starting material: identity and ratio of starting materials.
- And their manufacturing process: steps of the process, reaction type, process conditions (solvent, temperature, pressure…)

In addition, every known constituent needs to be reported.
Constituents which are unknown need to be identified as far as possible by a generic entry describing their chemical nature.

Substance identification

3) Data must be consistent through IUCLID sections 1.1, 1.2 and 1.4

Common inconsistencies:

- Identifiers refer to different substances (e.g. IUPAC name does not match the structural formula)
- The composition in section 1.2 is not consistent with quantitative analysis in 1.4
- Concentration ranges of constituents too broad (e.g. 30%<C<70% or C>75%) ➧ possibly more than 1 substance covered.

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Overall recommendations

1) **Justify in detail data waivers and alternatives to testing**.

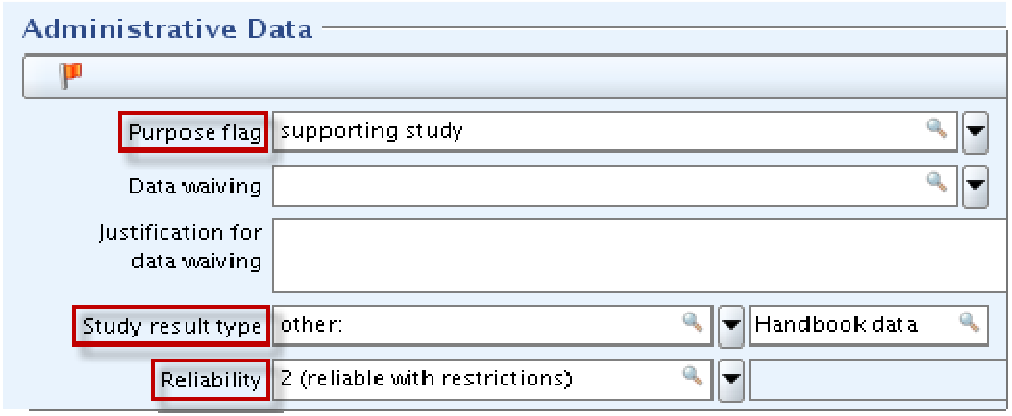
2) **Avoid submitting data in a data waiving record**. An endpoint study record with a selection done in field 'Data waiving' should only contain information in the field 'Justification for data waiving'. Any other data supporting this data waiving (such as QSARs, read-across, reference to a public report…) should be summarised in a separate endpoint study record (which could be flagged as 'Weight of evidence' or as 'supporting study').

Overall recommendations

3) **Submit information in IUCLID in a structured way**:

- Avoid adding information in free text fields, unless necessary. Instead try to use most of the IUCLID pick-lists and tables.

4) **Fill in the administrative part for each endpoint study record.** For all records (except Data waiving and Testing proposal), it is recommended to fill in at least the 'Purpose flag', 'Study result type' and 'Reliability':



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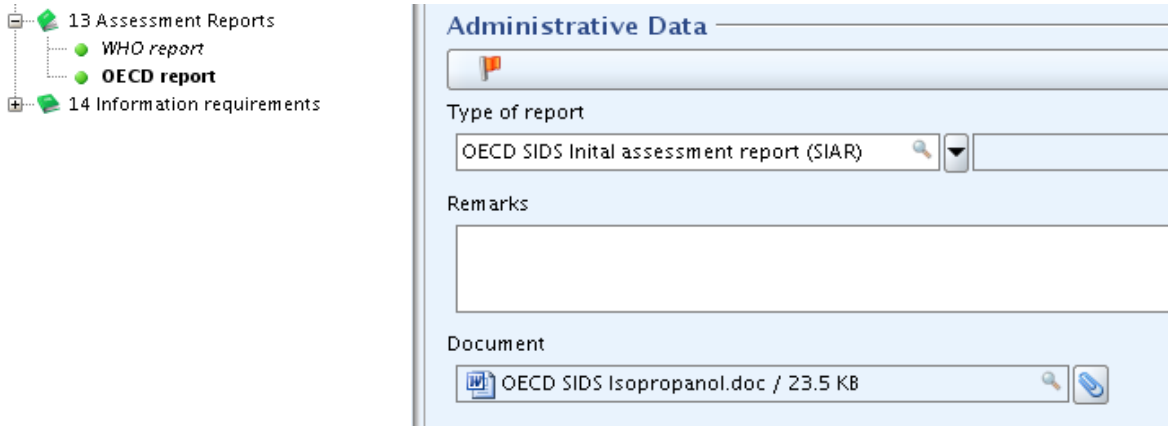
Robust study summaries

1) Robust study summaries must be given for **each Key study and each Experimental study that are part of a Weight of evidence approach**.

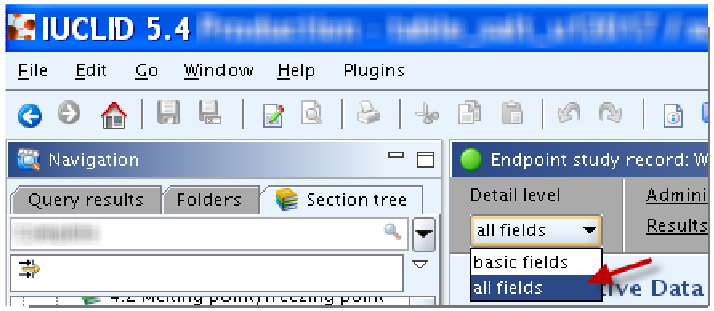
2) References to **scientific papers** or to **assessment reports by other bodies** (e.g. in a report from OECD, WHO, IARC…) are not sufficient. Relevant studies have to be summarised in detail in a (robust) study summary.

   - Assessment reports from other bodies should be attached in IUCLID section 13:

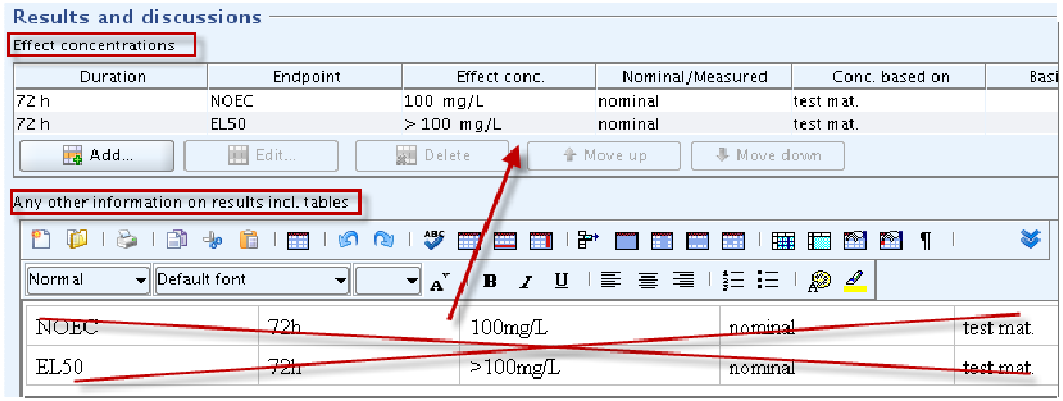


Robust study summaries

3) **All IUCLID fields of the endpoint study record should be filled in** for a Robust study summary (including species, route of exposure, test material). The detail level should be set up to 'all fields'. This will display basic fields and additional ones in blue.



4) Results should preferentially be reported in **tabular form**:



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Read-across

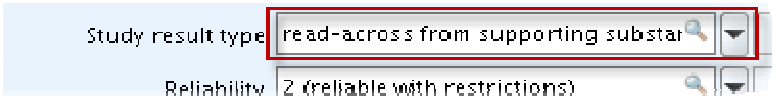
1) If an endpoint is covered by a read-across then the study performed on the source substance should be reported as a **Robust study summary**.

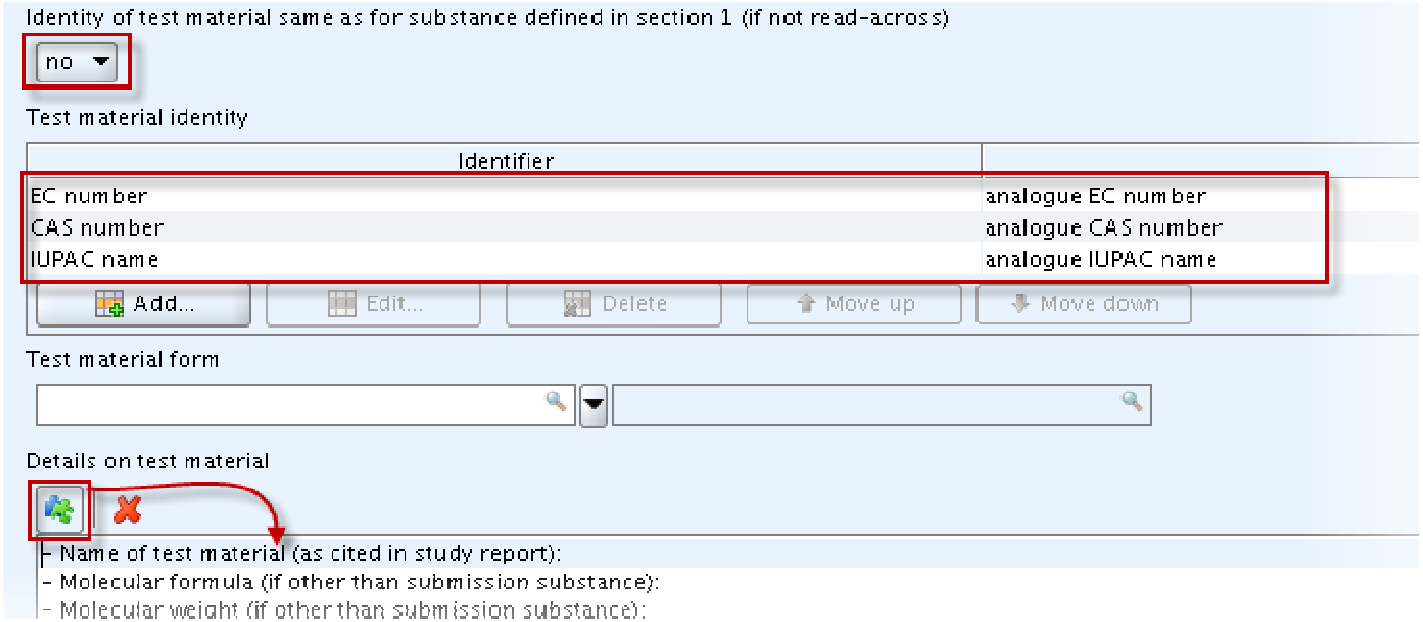
2) The read-across must be justified! This **Justification** (explanation/hypothesis) must detail:

   - Similarity (and dissimilarity):
     - of the target substance and the source substance (according to their functional groups)
     - of their metabolites/transformation products
   - Trend analysis and/or mechanistic considerations

3) This justification should be confirmed by **Supporting data** (e.g. experimental data, literature data).

Read-across

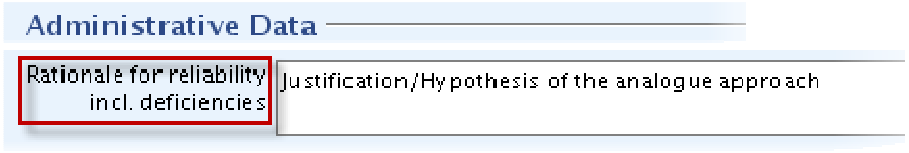

Study result type
read-across from supporting substar
Reliability
2 (reliable with restrictions)

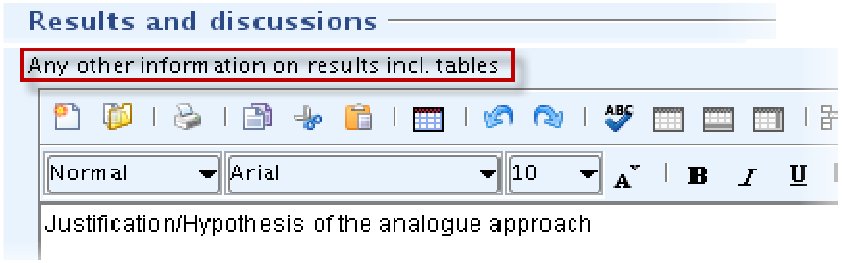

Identity of test material same as for substance defined in section 1 (if not read-across)
no
Test material identity
Identifier
EC number
analogue EC number
CAS number
analogue CAS number
IUPAC name
analogue IUPAC name
Add...
Edit...
Delete
Move up
Move down
Test material form
Details on test material
- Name of test material (as cited in study report):
- Molecular formula (if other than submission substance):
- Molecular weight (if other than submission substance):

Read-across

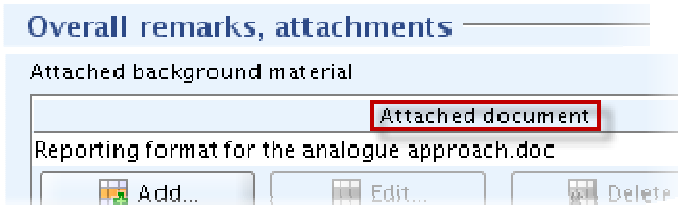
The **justification** of the read-across should be given:

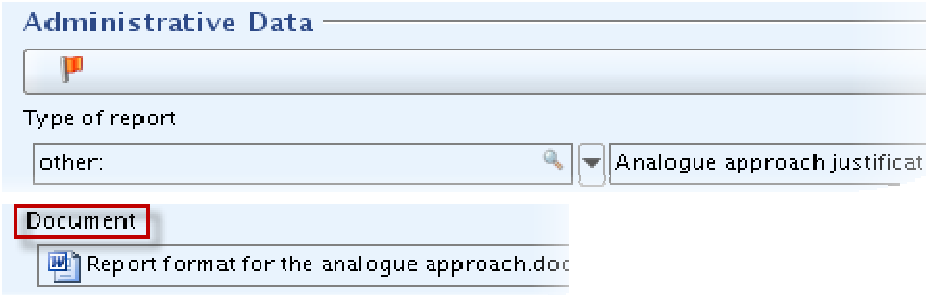
- in the following fields of the endpoint study record





- preferably also as an attachment (see 'Reporting format for the analogue approach' in Guidance on information requirements and chemical safety assessment - Chapter R.6 – Section R.6.2.6.1) under 'Overall remarks' or under section 13





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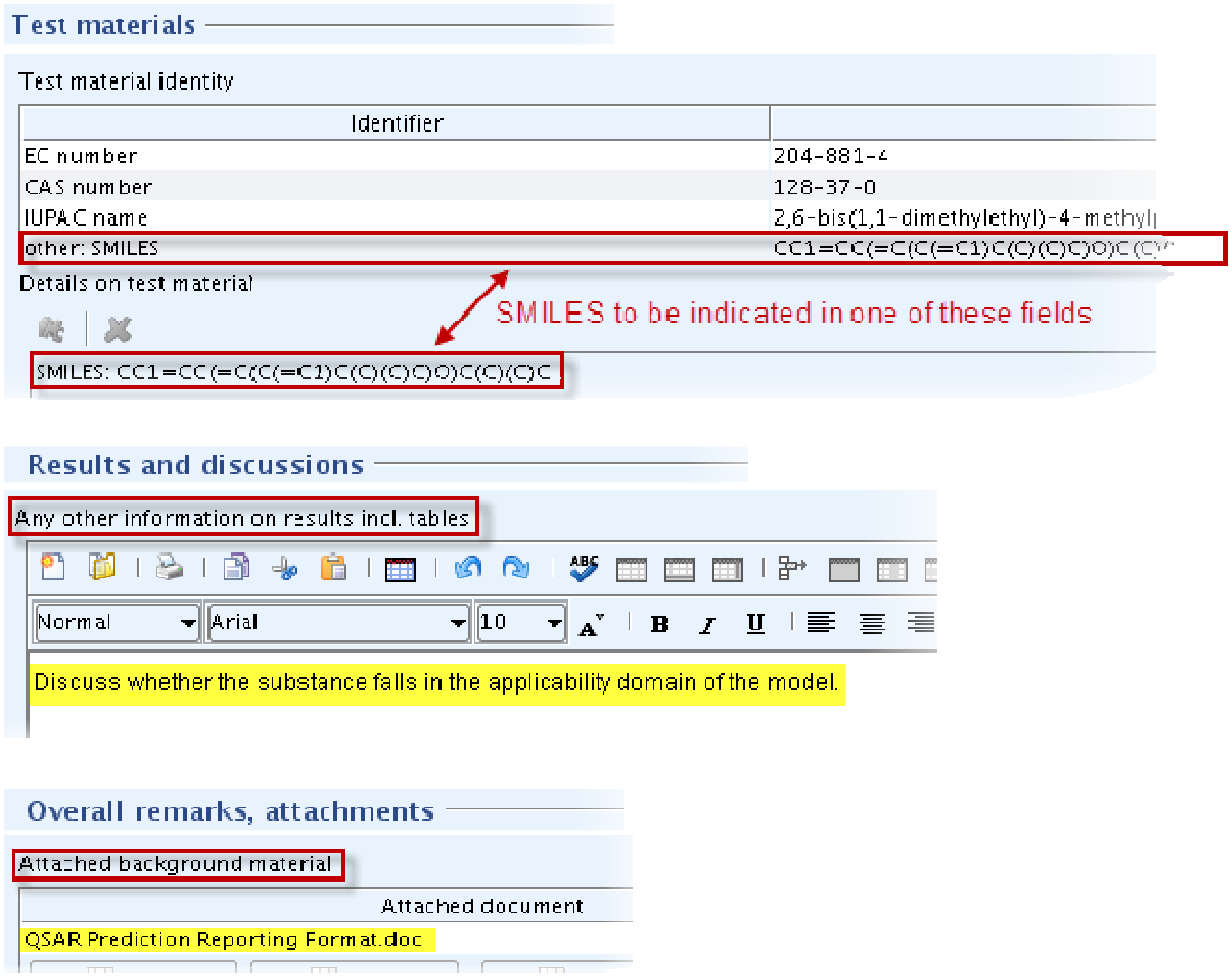
(Q)SAR

1) **A single (Q)SAR prediction can rarely be used instead of an experimental study.** It is more typically used as a supporting study or as part of a weight of evidence.

2) (Q)SARs are valuable only if conditions listed in REACH Annex IX-1.3 are fulfilled and documented by the registrant.
   - One of these conditions is that the registrant should demonstrate that the substance falls within the **applicability domain** (fragments, descriptors)

3) Each QSAR prediction should be **fully documented** in the IUCLID endpoint study record.


Test materials
Test material identity
Identifier
EC number
204-881-4
CAS number
128-37-0
IUPAC name
2,6-bis(1,1-dimethylethyl)-4-methyl
other: SMILES
CC1=CC(=C(C(=C1)C(C)(C)C)O)C(C)
Details on test material
SMILES to be indicated in one of these fields
SMILES: CC1=CC(=C(C(=C1)C(C)(C)C)O)C(C)(C)C
Results and discussions
Any other information on results incl. tables
Normal
Arial
10
Discuss whether the substance falls in the applicability domain of the model.
Overall remarks, attachments
Attached background material
Attached document
QSAR Prediction Reporting Format.doc

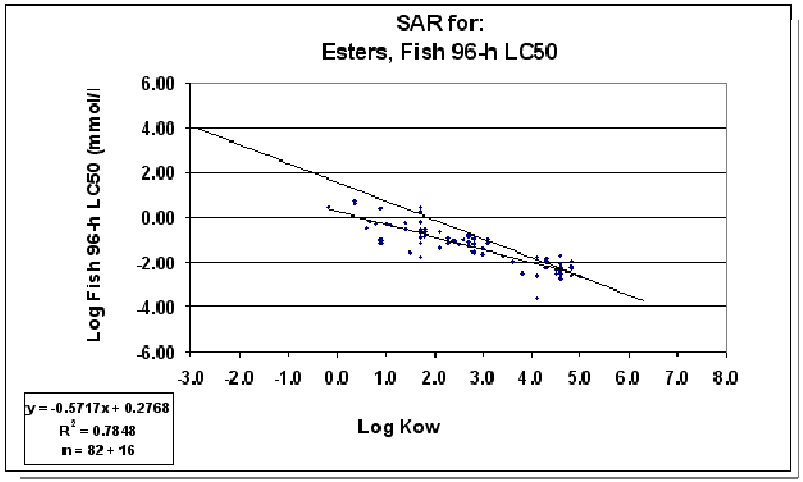
Applicability domain: Examples of conditions to be checked/reported.

- Does the substance contain fragments that are not represented in the training set?

NUM	LOGKOW FRAGMENT DESCRIPTION	
6	-CH2-	[aliphatic carbon]
2	-CH	[aliphatic carbon]
1	-NH-	[aliphatic attach]

- Do the descriptor values of the substance fall within defined ranges?

(e.g. ranges for Molecular weight,
Water solubility,
LogKow…)



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Weight of evidence

1) **Experimental studies** which are part of a weight of evidence approach should be reported as **Robust study summaries**.

2) All data that are part of the weight of evidence approach should have **'Purpose flag'='weight of evidence',** including data from handbooks, literature, (Q)SARs.

   - If some fields required by the Technical Completeness Check are irrelevant/unknown then 'Purpose flag' could be set as = **'supporting study'.**

Weight of evidence

3) Create an '**Endpoint study summary**' to document conclusion and justify the use of this approach instead of standard testing.

4) **'Data waiving'** should **not** be **mixed** with **'Weight of evidence'.**

- a Data waiving record should not contain data. Any data supporting the data waiving should be summarised in a separate endpoint study record (which could be flagged as 'Weight of evidence' or as 'supporting study').

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Chemical Safety Assessment

1) Ensure that your Classification and Labelling is done according to the **CLP Regulation**, and especially if your substance is already covered by an Harmonised C&L (see Annex VI, Tables 3.1 and 3.2 of CLP)

2) **Assessment factors** given in ECHA guidance should be used (default values). Any deviations from these recommended values must be justified.

   - For instance, assessment factors from other sources for deriving a DNEL should not be used without substance specific justification.

Chemical Safety Assessment

3) Identified uses are to be reported in section 3.5 of the IUCLID 5 dossier and in section 2.2 of the CSR. These brief general descriptions of uses must be consistent with the titles of the **exposure scenarios** in section 9.1 of the CSR.

   - Exposure scenarios covering too many uses often lead to unrealistic risk management recommendations.

4) All human health and environmental hazards should be covered by the **exposure assessment**, not only the ones leading to classification.

ECHA
EUROPEAN CHEMICALS AGENCY

Thank you
for your attention

ECHA Guidance material

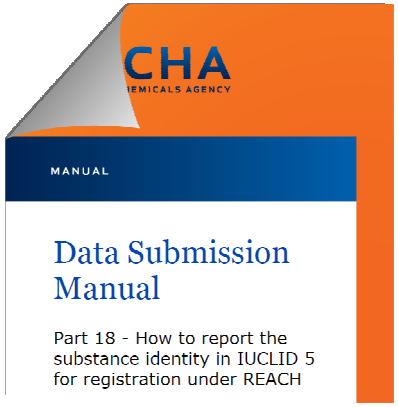
Substance identification

- Guidance Document for Substance Identification

http://echa.europa.eu/documents/10162/13643/substance_id_en.pdf

- Data Submission Manual 18

http://echa.europa.eu/documents/10162/13653/substance_id_report_iuclid_en.pdf



Endpoints

- Guidance document on Endpoint specific guidance (R.7)

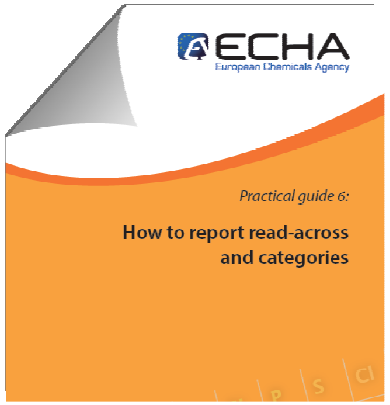
http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

- Guidance document on QSARs and grouping (R.6)

http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

- Practical guides 1, 2, 3, 4, 5 and 6

http://echa.europa.eu/web/guest/practical-guides



ECHA Guidance material

Chemical Safety assessment

- Chesar 2 user manuals

http://chesar.echa.europa.eu/web/chesar/support/manuals-tutorials

- Illustrative Chemical Safety Report

http://echa.europa.eu/documents/10162/13634/csr_illustrative+example_en.pdf

- Practical guide 14

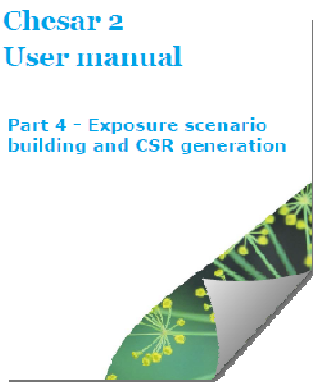
http://echa.europa.eu/documents/10162/13655/pg_14_on_hazard_endpoint_en.pdf

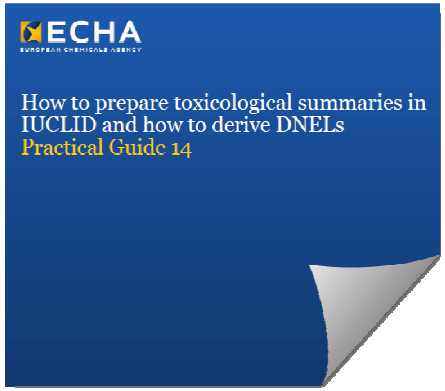
- Guidance document on Use descriptor system (R.12)

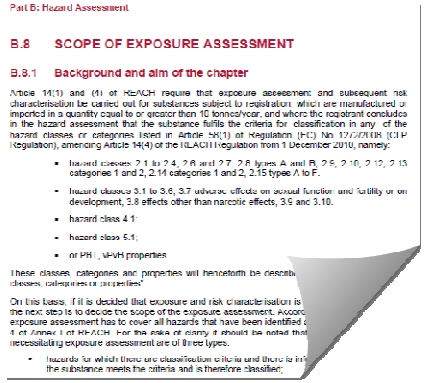
http://echa.europa.eu/documents/10162/13632/information_requirements_r12_en.pdf

- Guidance document on Hazard assessment (Chapter B.8)

http://echa.europa.eu/documents/10162/13643/information_requirements_part_b_en.pdf







ECHA Guidance material

General information

- Evaluation progress report 2011

http://echa.europa.eu/documents/10162/13560/mb_06_2012_general_report_2011_final_en.pdf

- Data Submission Manual 5

http://echa.europa.eu/documents/10162/13653/dsm5_tech_dossier_en.pdf

- FAQs about REACH section 6 and 11

http://echa.europa.eu/web/guest/support/faqs/frequently-asked-questions/frequently-asked-questions-about-reach

- IUCLID end user manual

This IUCLID end user manual is integrated in IUCLID software.

To obtain this information, place your cursor in a specific IUCLID field and press F1 on your keyboard. ⟶