How to bring your registration dossier in compliance with REACH – Tips and Hints

Higher Tier Human Health Studies

Kimmo Louekari
ECHA

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Higher Tier Human Health Studies
in the context of this presentation

Studies for	REACH Annex IX	IUCLID
Prenatal developmental toxicity, **PNDT** (Teratogenicity)	8.7.2	7.8.2
Repeated dose toxicity, **RDT** (Sub-chronic toxicity, 90-day)	8.6.2	7.4.1/2/3

Covering endpoints by adequate studies

Prenatal developmental toxicity

Required:

Study according to Method B.31 or Guideline OECD 414

Often found incompliance: Screening studies

Reproduction/Developmental Toxicity Screening Test (OECD 421)

Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD 422)

Prenatal developmental toxicity

Screening studies

provide initial information on possible effects on male and female reproductive performance, which is still insufficient at this tonnage

provide only very limited information on developmental toxicity

cannot be accepted for fulfilling REACH Annex IX 8.7.2 requirement

Required

studies according to Method B.31 or Guideline OECD 414

Repeated dose toxicity

Required:

Sub-chronic toxicity study (90-day), rodents

Often found incompliance: studies with duration less than 90 days

Short-term repeated dose toxicity study (28 days)

Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD 422)

Repeated dose toxicity

Studies with duration less than 90 days

provide initial information on possible health hazards likely to arise from repeated exposure, but are insufficient to cover the endpoint 90-day toxicity

cover repeated exposure for only a relatively limited period of time

cannot be accepted for fulfilling REACH Annex IX 8.6.2 requirement

Required

studies with test substance administration for 90 (or more) days, e.g. according to Method B.26 or Guideline OECD 408

Covering endpoints by adaptation/waiver

Adaptations that have been used for 90-day study and developmental toxicity study

Weight of evidence
Read-across or grouping
Exposure based waiving/adaptation

Substance is inert
Substance is corrosive
Immediate disintegration

Topic of this presentation

Etc.

Some registrants considered that the substance is chemically and toxicologically **inert/unreactive**

Specific adaptation for a 90-day study

According to **Annex IX, 8.6.2. Column 2** **no** sub-chronic toxicity study needs to be conducted **if:**

1. "the substance is **unreactive**, insoluble **and** not inhalable **and**
2. there is no evidence of **absorption and**
3. no evidence of **toxicity** in a 28-day 'limit test',
4. particularly if such a pattern is coupled with **limited human exposure**."

How to formulate an acceptable adaptation in that case, for the 90-day study?

At least **the first three** of these cumulative conditions need to be supported by data
i.e. the claim that the substance is inert or unreactive is **not sufficient**.

When the registrant has not provided sufficient information to show that conditions of an adaptation in Column 2 of Annex IX, 8.6.2. or Annex XI are met, the adaptation cannot be accepted by ECHA.

General adaptation for a 90-day study and for PNDT

Weight of evidence (WoE)

According to **Annex XI, 1.2**:

"There may be sufficient evidence from **several independent sources of information** leading to the assumption/conclusion that **a substance has or has not a particular dangerous property,** while the information from each **single source alone is regarded insufficient** to support this notion."

In the case of an unreactive or inert substance, other potentially useful information might consist of:

- **Low absorption and**
- **Low toxicity (acute or sub-acute toxicity)**
- Information of a related substance or from a group on the endpoint

- Note that the focus has to be on meeting the information requirements for the respective endpoint, e.g. the key parameters need to be covered.

What would not be sufficient

- To adapt this standard information requirement on the basis of **inertness only**:

=> **Neither** column 2 of Section 8.6.2., Section 8.7.2 **nor** general rules for adaptation in Annex XI include this possibility.

- According to Annex IX, 8.6.2. column 2, "no-absorption" and "no toxicity in 28-day toxicity study" need to be verified together with unreactive nature of the registered substance.

Adaptation for a prenatal developmental toxicity study

Column 2 of Annex IX, 8.7. does not include a possibility to adapt this information requirement based on **inertness.**

Weight of evidence according to **Annex XI, 1.2:**
may be proposed when there is sufficient evidence from **several independent sources of information…"**

In the case of an unreactive or inert substance, other potentially useful information might consist of:

- Evidence of **low absorption and**
- Evidence of **low toxicity (acute or sub-acute)**

This information needs to be given in the study records.

The registrant considered that the substance is **corrosive**

According to the **introductory paragraph 4 of Annex IX and X** of the REACH Regulation "*in vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided".

However, **non-corrosive concentrations can be tested**.

Introductory paragraph 4 is not a legal basis for adapting standard information requirements.

Sub-chronic toxicity study (90-day) prenatal developmental toxicity study

- There is **no acceptable waiver that is based only on corrosivity**.
- The registrant is advised to select the concentrations of the test substance in order to avoid corrosion allowing at the same time detection of potential systemic toxicity effects of the substance.
- The general principle to avoid corrosion and irritation is set out in the relevant *test guidelines.*

The registrant considered
that the substance
immediately disintegrates
and therefore testing
can be waived

Specific adaptations for sub-chronic toxicity study (90-day)

According to **Column 2 of REACH Annex IX, 8.6.2.**
no sub-chronic toxicity study needs to be conducted if:

1. "a substance undergoes immediate disintegration **and**

2. there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake)".

Both conditions of that adaptation need to be fulfilled.

How to formulate an acceptable adaptation for the 90-day study?

1. Immediate disintegration

- For example, the rate of hydrolysis or disintegration needs to be documented, usually based on experimental data.
That can be given within the physico-chemical sections, i.e. section 4 in the IUCLID dossier.

2. Data on cleavage products

- Toxicity and other data on "cleavage products" can be from different sources of data (experimental, modelling, human data etc.).
For the 90-day toxicity study, the data should be given in section 7.5 in the IUCLID dossier.

- If the cleavage products are physiological constituents, and their absorbed quantities are estimated, the need for experimental data may differ from other type of substances.

The registrant considered that **testing is technically not possible** and therefore testing can be adapted/ waived

According to **section 2 of Annex XI**, "testing for a specific endpoint may be omitted, if it is technically not possible to conduct the study as a consequence of the properties of the substance: e.g.

- **highly reactive or**
- **unstable substances cannot be used**,

or mixing of the substance with water may cause danger of fire or explosion or the radio-labelling of the substance required in certain studies may not be possible."

This is a generic possibility for adaptation.

How to formulate an acceptable adaptation when **testing is technically not possible**

In section 4 in the IUCLID dossier, the registrant should provide data on the relevant physico-chemical properties that proves that the testing is technically not possible.

The justification/explanation why testing (for repeated dose and/or developmental toxicity) is not possible needs to address the specific test guidelines and conditions applied in them.

Summary

- **Inertness** of the substance is not an acceptable waiver alone; e.g. low toxicity and low absorption need to be demonstrated.
- **Corrosivity** of the substance is not an acceptable waiver; usually corrosive substances should be tested in non-corrosive concentrations.
- **Immediate disintegration** of the substances, when the toxicity of the cleavage products has been characterised, is a valid adaptation.

Thank you