How to bring your registration dossier in compliance with REACH – Tips and Hints (Part 3)

Higher tier human health studies

14th May 2013

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Higher tier human health studies
in the context of this presentation

Studies for	REACH Annex IX	IUCLID
Repeated dose toxicity, **RDT** (Sub-chronic toxicity, 90-day) *for example Method B.26 or Guideline OECD 408*	8.6.2	7.4.1/2/3
Prenatal developmental toxicity, **PNDT** (Teratogenicity) *Method B.31 or Guideline OECD 414*	8.7.2	7.8.2
Two-generation reproductive toxicity, **2-gen** *Method B.35 or Guideline OECD 416 or Guideline OECD 443 including the extension of Cohort 1 B to mate the F1 animals to produce the F2 generation, which shall be kept until weaning*	8.7.3	7.8.1

Covering endpoints by adaptation/waiver

Adaptations that have been used for repeated dose toxicity, developmental toxicity and or two-generation reproductive toxicity

Weight of evidence

Read-across or grouping

Exposure based waiving/adaptation

Topic of this presentation

Substance is inert

Substance is corrosive

Immediate disintegration

Topic of last presentation on 28 January 2013

Exposure based adaptations, EBAs

An EBA "is a deviation from the standard information requirement at the actual tonnage level based on exposure arguments.

The terminology 'adaptation' comprises all types of modifications of the standard information requirements, including omissions, triggering, replacement or other adaptations."

Guidance on information requirements and chemical safety assessment, Chapter R.5: Adaptation of information requirements, Version 2.1 – December 2011

Basis for EBAs

1. Omission of testing based on column 2 of Annexes IX and/or X, or
2. Omission of testing based on the general rules for adaptation of the standard testing regime laid down in Annex XI section 3

- Any adaptation for a specific endpoint has to be documented in the IUCLID 5 dossier. When the argumentation is built on the use of exposure scenarios and related exposure estimates, the documentation in IUCLID 5 has to refer to the chemical safety report.

Column 2 adaptations

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

It has to be supported by **data** that the substance is *unreactive, insoluble and not inhalable.* Data can be given within the physico-chemical sections, i.e. section 4 in the IUCLID dossier.

It has to be **documented** that there is *no evidence of absorption.*

It has to be **documented** that there is no evidence of toxicity in a 28-day repeated dose toxicity study (or in a study with longer duration) at a dose of 1 000 mg/kg body weight and day or higher.

Information on **limited human exposure** should to be provided. This information shall be in accordance with the PROCs given by the registrant.

All of these four conditions need to be documented.

How to formulate an acceptable adaptation in that case, for reproductive toxicity studies?

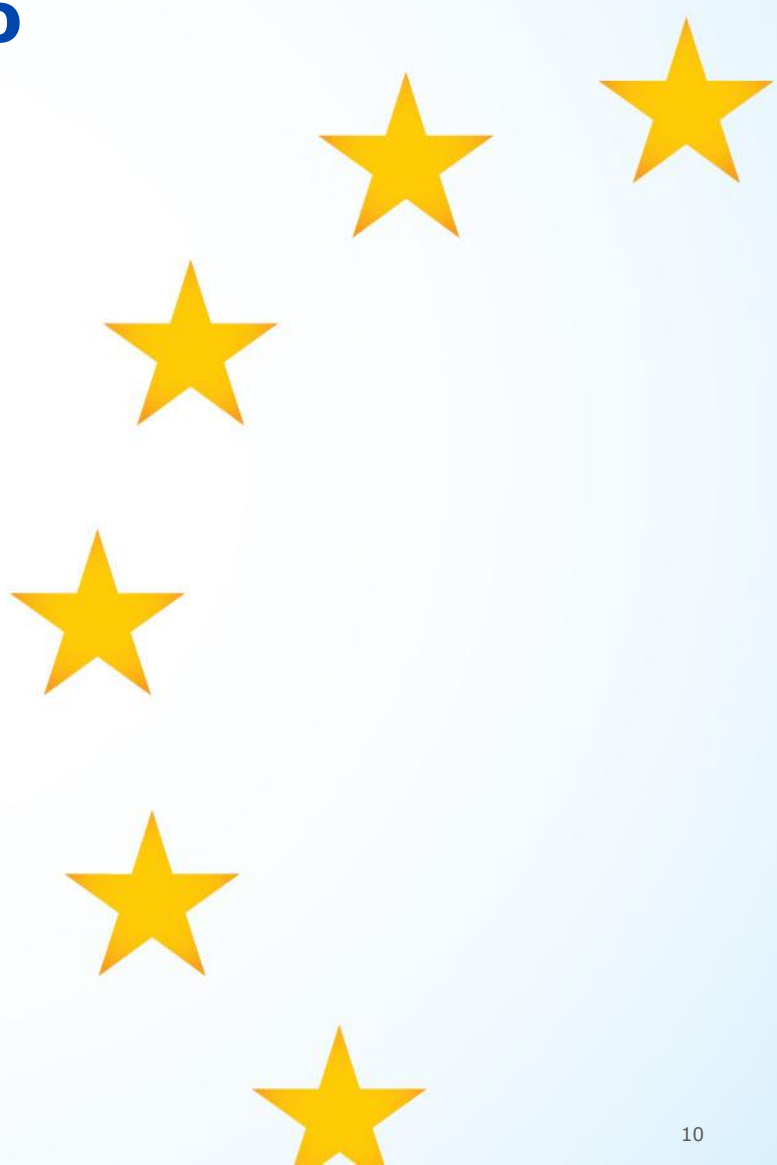
It has to be **documented** that there is *no evidence of toxicity seen in any of the tests available.*

It has to be **documented** by toxicokinetic data that **no** systemic absorption occurs via relevant routes of exposure. The data shall include evidence that neither the substance nor its metabolites are present in urine, bile or exhaled air.

Information on **no or no significant human exposure** has to be provided. This information shall be in accordance with the PROCs given by the registrant.

All of these three conditions need to be fulfilled.

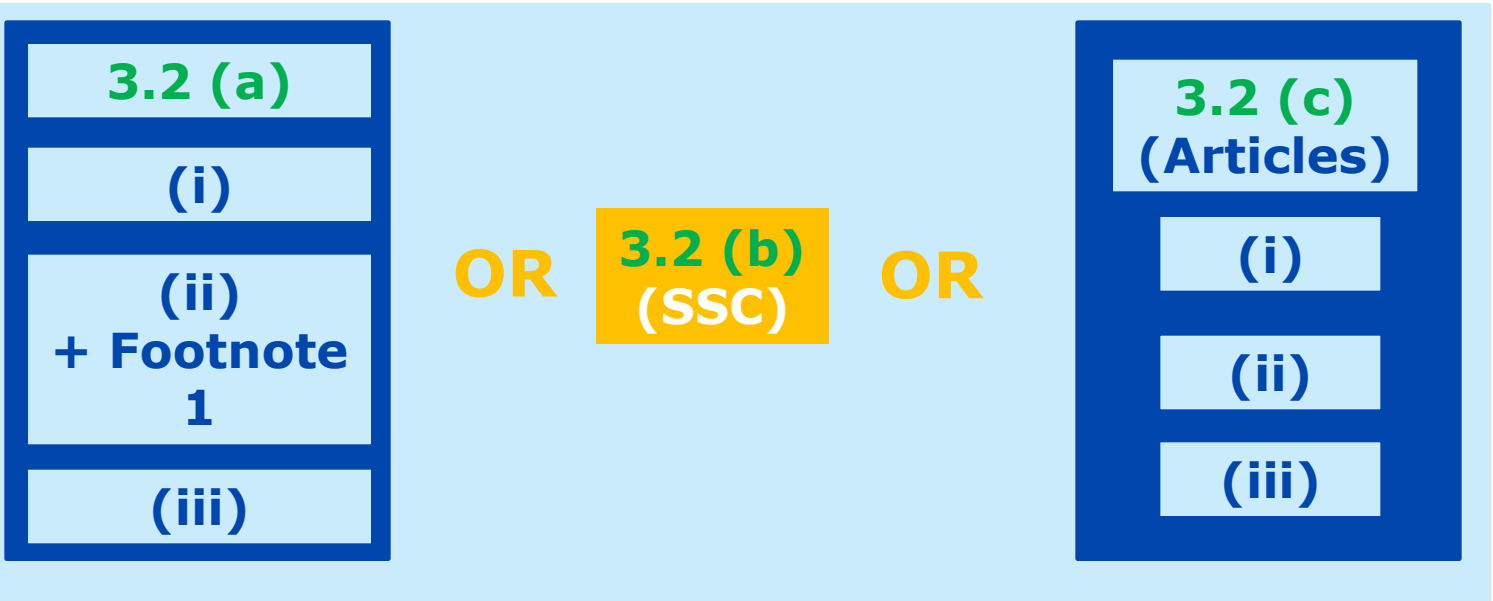
Adaptations according to Annex XI section 3



Annex XI, 3. Substance-tailored exposure-driven testing

3.1: Introduction, general statement

AND



AND

3.3: Communication through supply chain

Annex XI, 3.1

"Testing in accordance with Sections 8.6 and 8.7 of Annex VIII and in accordance with Annex IX and Annex X may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report."

- This section is an introduction to items 3.1 to 3.3 and cannot be taken as a "stand-alone" adaptation.
- When adaptations are made according to Annex XI, section 3, it is mandatory that exposure scenarios are developed in the chemical safety report, even if the substance is not classified.

Annex XI, 3.2

In all cases, adequate justification and documentation shall be provided. The justification shall be based on a thorough and rigorous exposure assessment in accordance with section 5 of Annex I and shall meet any one of the following criteria:

- REACH Annex XI, 3.2. lists three criteria (a, b and c) which are presented on the following slides

Annex XI, 3.2 (a), (a)(i)

(a) the manufacturer or importer demonstrates and documents that **all** of the following conditions are fulfilled:

(i) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5;

- As stated before, it is mandatory that exposure scenarios are developed in the chemical safety report, even if the substance is not classified.

Annex XI, 3.2 (a)(ii)

(ii) a DNEL …can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes ([1]).

- Annex XI, 3.2 (a)(ii) refers to a **footnote**, given on the following slide. This footnote is essential for using these adaptation possibilities.

Annex XI, 3.2 (a)(ii), footnote 1

"For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of Section 8.7 of Annexes IX and X, a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study.

For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of section 8.6 of Annexes IX and X, a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study."

- **This footnote makes it very difficult to waive a 90-day study/a PNDT/a two-generation study based on an adaptation which refers to Annex XI, 3.2 (a).**

Annex XI, 3.2 (a)(iii)

"(iii) the comparison of the derived DNEL or PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC; "

- **Summary Annex XI, 3.2 (a):**
  Even if absence of or no significant exposure can be demonstrated and even if RCRs derived from DNELs from screening studies or 28-day toxicity studies are well below 1, footnote 1 makes it **very difficult** to waive a 90-day-study, a developmental toxicity study or a reproductive toxicity study.
- Read-across or using e.g. a chronic toxicity study to waive the 90-day study might be possible under this provision, but if these are acceptable, the EBA is no longer necessary.

Annex XI, 3.2 (b)

"(b) where the substance is not incorporated in an article the manufacturer or importer demonstrates and documents for all relevant scenarios that throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f) apply;"

- Without a detailed process description, ECHA cannot assess/verify the SCCs are applied (see the next slide also).
- This information shall be in accordance with the PROCs given by the registrant.
- In some cases, it has been found that the PROCS given in the registration are not compatible with the SCCs and therefore the adaptation is not possible.

SCCs as described in Article 18(4)a-f of REACH

(a) the substance is rigorously contained… during its whole lifecycle…

(b) procedural and control technologies shall be used that minimise emission and any resulting exposure

(c) only properly trained and authorised personnel handle the substance

(d) special procedures are applied for cleaning and maintenance works

(e) in cases of accident… procedural and/or control technologies are used to minimise emissions and the resulting exposure…

(f) substance-handling procedures are well documented and strictly supervised by the site operator

Note also that the downstream uses need to be covered.

Annex XI, 3.2 (c)

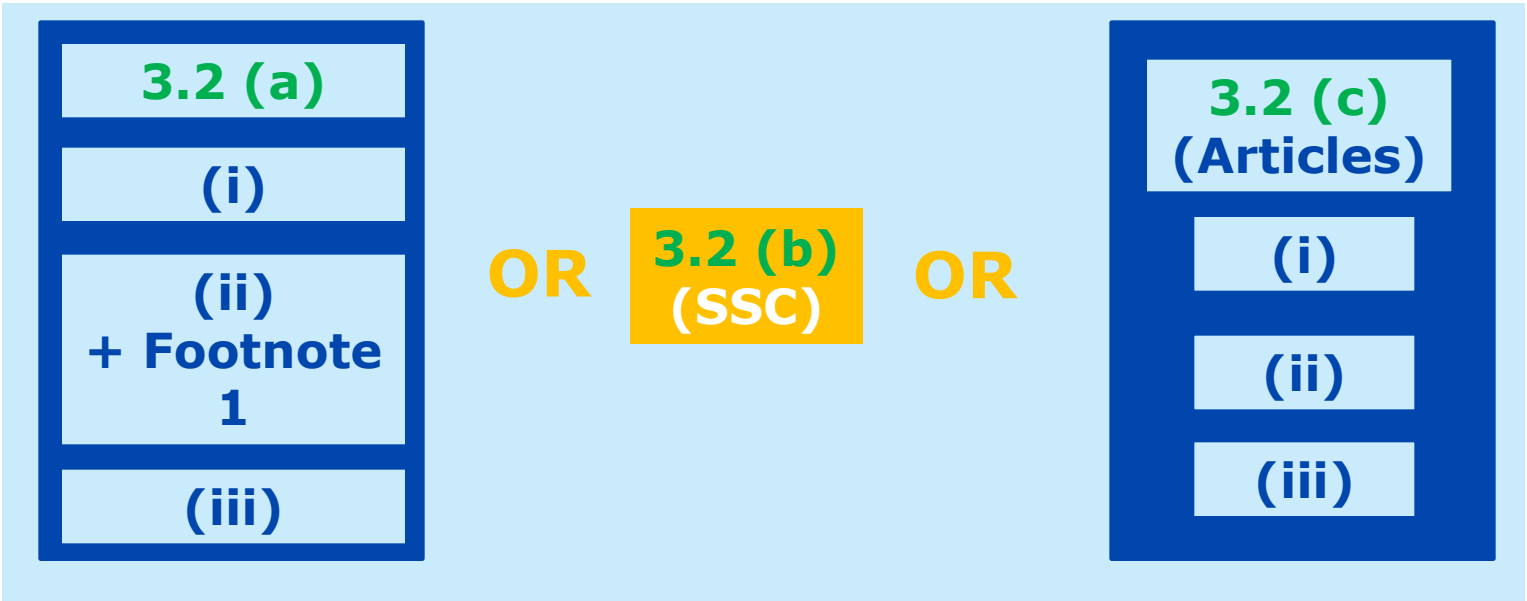
(c) where the substance is **incorporated in an article** in which it is permanently embedded in a matrix or otherwise rigorously contained by technical means

This adaptation is not within the scope of this presentation

Annex XI, 3. Substance-tailored exposure-driven testing

3.1: Introduction, general statement

AND



AND

3.3: Communication through supply chain

Summary

- Exposure based adaptations (EBAs) can be made based on **column 2** of Annexes IX and X or on **Annex XI, section 3**.
- For all adaptation possibilities, **cumulative conditions apply** and **all of them** have to be met.
- **EBAs for higher tier human health studies based on Annex XI, 3.2(a) are close to impossible** due to 3.2(a)(ii) footnote 1.
- If EBAs are based on Annex XI, section 3, **exposure scenarios** have to be developed in the chemical safety report.
- The registrant shall **clearly indicate** which adaptation is addressed for the respective endpoint (e.g. “Annex XI, 3.2.(b)”).

How to comply with EBA requirements

- Document that all **cumulative conditions** are met.
- If **SCCs** (the most promising and perhaps the only acceptable EBA) can be applied, provide detailed process descriptions and check the PROCs/uses.
- Besides EBAs, also consider other adaptation possibilities, e.g. read-across or weight of evidence, and provide proper documentation.

Thank you