How to bring your registration dossier in compliance with REACH

Tips and Hints - Part 5

Higher Tier Human Health II

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Content of the presentation

- Endpoints covered
- Types of shortcomings
- Advice and recommendations to the Registrants

The higher tier human health endpoints

In this presentation three **endpoints** are covered

- sub-chronic toxicity
- pre-natal developmental toxicity and
- two-generation reproductive toxicity

Three types of **adaptations to the standard testing regime** suggested for these endpoints were evaluated

- The substance is “toxicologically inert”
- The substance is “corrosive”
- Only a screening study provided for an Annex X dossier

The substance is “toxicologically inert”

According to Annex IX Section 8.6.2, column 2, in order to apply this adaptation for **sub-chronic toxicity**, the Registrant has to show that four criteria are met

1. **“the substance is unreactive, insoluble and not inhalable”**

- Solubility and bioaccessibility studies may be useful in this regards as well as specification of the physical-chemical characteristics of the substance, also data on particle size distribution may be necessary

2. **“and there is no evidence of absorption”**

- Toxicokinetic studies, in vitro studies on absorption or bioavailability studies may provide relevant evidence

The substance is “toxicologically inert” (2)

3. “and no evidence of toxicity in a 28-day ‘limit test’

- In practice, the sub-acute study is necessary to demonstrate this

4. “particularly if such a pattern is coupled with limited human exposure.”

- This point is not an absolute requirement, but may become necessary if the Registrant applies a similar adaption for the pre-natal developmental toxicity

The substance is “toxicologically inert”

According to Annex IX Section 8.7, column 2, in order to apply this adaptation for **pre-natal developmental toxicity and/or two-generation reproductive toxicity**, the Registrant has to show that

“ there is no systemic absorption occurs via relevant routes”

- Toxicokinetic studies, in vitro studies on absorption or bioavailability studies may provide relevant evidence

“the substance is of low toxicological activity”

- A sub-acute studies may be necessary to demonstrate this; Weight of Evidence approach/analysis based on several studies may also be an option

“there is no or no significant human exposure”

- Exposure scenarios and or exposure estimates need to be developed to demonstrate that this criteria is met.

The substance is “corrosive”

Neither column 2 of Annex IX, 8.7.2. nor the general rules for adaptation of Annex XI include such possibility to adapt standard information requirement for **sub-chronic toxicity** or for **pre-natal developmental toxicity**.

Corrosivity of the substance can not alone be used when as a waiver/adaptation.

In case a corrosive substance is e.g. an inorganic compound that rapidly disintegrates or decomposes, some other adaptions may be developed.

Only a screening study provided for an Annex X dossier

Several dossier were filtered, where the Registrant has provided only a developmental screening study (OECD 421 or 422) in order to meet the information requirement for **pre-natal developmental toxicity study** (OECD 414) or **two-generation reproductive toxicity** (OECD 416)

In these cases, ECHA has found that

- Dossiers which neither contain a waiver nor a testing proposal, but cover that endpoint by inadequate studies like developmental screening studies (OECD 421 or 422) are subject to a CCH Draft Decision to submit the missing standard information

- Thus, this type of adaptation will not be acceptable

Summary

For these three endpoints, in case the Registrant suggests an adapation based on

- **The substance being "toxicologically inert"**, he needs to meet the specific Annex IX, column 2 criteria with reliable and relevant data
- **"Corrosivity",** he needs to acknowledge that this is not a valid adaptation, because non-corrosive concentrations can be applied

In case the Registrant **only provided a reproductive/developmental toxicity screening study** in a Annex IX or X dossier, he needs to acknowledge that the definitive studies (OECD 414 and/or 416) will be requested by ECHA

Questions?

To the Q&A panel (between 11:00 and 13:30, Helsinki time), or

To the ECHA helpdesk (any time): http://echa.europa.eu/contact/helpdesk-contact-form