Information requirements for reproductive toxicity under REACH

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Information requirements for reproductive toxicity under REACH

1 – 10 tonnes per year (Annex VII)

- none

10 – 100 tonnes per year (Annex VIII)

- Screening for reproductive/developmental toxicity (OECD 421 or 422)

100 – 1000 tonnes per year (Annex IX)

- Pre-natal developmental toxicity study (first species)
- Two-generation reproductive toxicity study (if concern)

Over 1000 tonnes per year (Annex X)

- Pre-natal developmental toxicity study (first species)
- Pre-natal developmental toxicity study (second species)
- Two-generation reproductive toxicity study

ANNEX VIII (10 – 100 tonnes per year)

8.7.1 Screening for reproductive/developmental toxicity

- one species
- (OECD 421 or 422)
- if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant

ANNEX IX (100 – 1000 tonnes per year)

8.7.2. Pre-natal developmental toxicity study

- one species [*first species*],
- most appropriate route of administration, having regard to the likely route of human exposure
- (B.31 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 414).

8.7.3. Two-generation reproductive toxicity study,

- one species, male and female,
- most appropriate route of administration, having regard to the likely route of human exposure,
- if the 28-day or 90- day study indicates adverse effects on reproductive organs or tissues.

ANNEX X (over 1000 tonnes per year)

8.7.2. Pre-natal developmental toxicity study

- one species [*first species*],
- most appropriate route of administration, having regard to the likely route of human exposure
- (B.31 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 414).

8.7.2. Developmental toxicity study

- one species [*second species*],
- most appropriate route of administration, having regard to the likely route of human exposure
- (OECD 414).

8.7.3. Two-generation reproductive toxicity study,

- one species, male and female,
- most appropriate route of administration, having regard to the likely route of human exposure,
- unless already provided as part of Annex IX requirements.

REACH strategy to cover an information requirement

Reproductive toxicity study available

- Registrant to assess the quality of the study

Reproductive toxicity study not available

- Registrants to assess if further testing is required
  ➔ testing proposal for ECHA to evaluate
- Registrants to assess if further testing is not required: use of adaptation possibilities

Reproductive toxicity study available

Reliable study performed *according to the test method* indicated in the test method regulation and *according GLP*

- Study can be used for DNEL derivation and risk assessment (*see further slides*)

Study performed not according to the (latest) test method indicated in the test method regulation or not according to GLP

- Evaluation of the study if the key parameters of the study required for this endpoint are adequately covered (Annex XI, 1.1.2)
- Study might be used in a weight of evidence approach together with further information (Annex XI, 1.2)

DNEL derivation and risk assessment (I)

No-Adverse Effects Levels (NOAELs) from the study/ies for

- developmental toxicity
- fertility

Derived No-Effect Levels (DNELs)

- Point of departure: lowest NOAEL identified for an endpoint
- Different DNELs:
  - populations: workers and general population
  - routes of human exposure: inhalation, dermal, (oral)
  - duration of exposure: acute and long-term
  - systemic and local effects
- Assessment factors
  - inter- and intra-species variability
  - exposure duration
  - dose-response
  - quality of database

DNEL derivation and risk assessment (II)

Exposure assessment

Determination of occupational exposure and risk management measures (RMMs) for each exposure scenario

- Tier 1 exposure scenario: exposure model (very often ECETOC TRA)
  - physical properties of the substance and products handled
  - level of containment
  - presence or absence of local exhaust ventilation (LEV)
  - duration of activity
  - personal protection equipment (PPE)
  - limitations of the model to be considered; e.g.
    - cannot be used for aerosol generation
    - poor prediction for dermal route;
      especially if substance is easily absorbed via the skin
- Tier 2 exposure scenario: refined exposure assessment based on measured exposure data

DNEL derivation and risk assessment (III)

Risk characterisation

Risk Characterisation Ratio (RCR): quotient of exposure level and DNEL

- RCRs for all exposure scenarios
- RCRs for individual routes and for combined routes
- RCRs need to be below 1!
- If a RCR is above 1, refinement of exposure assessment necessary

Reproductive toxicity study *not* available

Registrant decides that testing is necessary

- Initiate testing immediately: screening studies
- Make a “Testing Proposal” which is evaluated by ECHA:
  - pre-natal developmental toxicity study
  - 2-generation reproductive toxicity study

Registrant decides that testing is *not* necessary

adaptation = waiving of the study (see following slides)

- Specific adaptations according to Column 2 of the information requirement
- General adaptation possibilities according to Annex XI

General adaptation possibilities (Annex XI)

- Annex XI, 1.1.2.: Use of available information not performed according to test methods indicated or GLP
- Annex 1.2.: Weight of evidence
- Annex 1.5.: Grouping of substance and read-across
- Annex XI, 3.: Exposure based adaptations

Exposure based adaptations (Annex XI, 3.)

3.1. Testing … may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report.

3.2. … justification … based on a thorough and rigorous exposure assessment … and shall meet any one of the following criteria:

a) … all of the following conditions are fulfilled:
   i. … absence of or no significant exposure in all scenarios …
   ii. a DNEL … can be derived from results of available test …
   Footnote: DNEL from screening study not appropriate
   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 …

b) substance is not incorporated in an article … throughout the life cycle strictly controlled conditions … apply;

c) … substance is incorporated in an article … all of the following conditions are fulfille
   i. The substance is not released during its life cycle;
   ii. The likelyhood that workers or general public or environment are exposed … is negligible; and
   iii. The substance is handled according … Article 18(4)(a) to (f)….

Specific adaptation possibilities (Annex IX/X, 8.7., Column 2) (I)

The studies do not need to be conducted if:

- the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or
- the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or

Specific adaptation possibilities (Annex IX/X, 8.7., Column 2) (II)

The studies do not need to be conducted if:

- the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.

Specific adaptation possibilities (Annex IX/X, 8.7., Column 2) (III)

The studies do not need to be conducted if:

- If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for developmental toxicity must be considered.

Specific adaptation possibilities (Annex IX/X, 8.7., Column 2) (IV)

The studies do not need to be conducted if:

- If a substance is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.

Compliance check of registrations (1)

Article 41

1. The Agency may examine any registration in order to verify any of the following:

- (a) that the information in the technical dossier(s) submitted pursuant to Article 10 complies with the requirements of Articles 10, 12 and 13 and with Annexes III and VI to X;
- (b) that the adaptations of the standard information requirements and the related justifications submitted in the technical dossier(s) comply with the rules governing such adaptations set out in Annexes VII to X and with the general rules set out in Annex XI;
- (c) that any required chemical safety assessment and chemical safety report comply with the requirements of Annex I and that the proposed risk management measures are adequate;

Compliance check of registrations (2)

End of 2012 number of active registrations was about 28000.

More than 16000 phase-in registrations above 1000 tonnes

ECHA performed more than 1100 compliance checks by end of 2013.

For the endpoint pre-natal developmental toxicity study and/or two-generation reproductive toxicity study ECHA observed the following incompliances, e.g.:

- Endpoint(s) covered by a screening study (OECD 421 or 422);
- Specific column 2 adaptation of Annex IX/X, 8.7. not fulfilled (no toxicity, no absorption, no human exposure);
- General adaptation possibilities not fulfilled, e.g. read-across not plausible and /or not justified.

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