REACH revision

Changes in Standard Information Requirements and Annex XI: Status & implications

NAM workshop 31/5 – 1/6

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CSS goal: Increase information requirements for low tonnages, identify most harmful substances

Increase information
- for low tonnage substances

- to identify most harmful substances including endocrine disruptors

- Reduce the need for animal testing, if possible, by including **NAMs**

- Need to take proportionality considerations into account (low tonnages)

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Increase information requirements for low tonnages, identify most harmful substances - Human health / ED

- **New NAM requirements in Annex VII under consideration:**
  - in vitro cytotoxicity (Neutral Red Uptake Assay) + QSAR (CATMoS model)

  - toxicokinetics & ADME → to facilitate read-across
    in chemico protein binding (e.g., fraction unbound in human plasma)
    in vitro human hepatic clearance (e.g., isolated human hepatocytes)
    in vitro intestinal absorption (e.g., Caco-2 permeability)

  - ED In vitro mechanistic information (relevant for HH and ENV)
    Estrogen receptor transactivation assay (OECD TG 455)
    Androgen receptor transactivation assay (OECD TG 458)
    H295R steroidogenesis assay (OECD TG 456)
    Aromatase assay (OPPTS 890.1200)

Increase information requirements for low tonnages, identify most harmful substances - Human health

- **Information critically lacking for the 5 800 Annex VII substances is repeated dose toxicity and reproductive/developmental toxicity**

- No NAMs available for regulatory use yet
- Consideration to require the combined study (**OECD TG 422**) for low tonnages
- only for substances able to exert such hazard, i.e., that have sufficient half-life in the body:

  waiving in case of insufficient predicted half-life

  - phys-chem properties e.g., log Kow (> cut-off)
  - in vitro toxicokinetics data
  - in silico predictions

  (waiving conditions to be defined still)

Increase information requirements for low tonnages via NAMs - Environment

- **Replacing short-term fish toxicity test with**:

  - In vitro cytotoxicity (OECD TG 249) or fish embryo toxicity (OECD TG 236)

- **Move from Annex IX to Annex VII:**

  - Long-term toxicity testing on invertebrates (Daphnia)

Amend information requirements with NAMs - Environment

Replacing bioaccumulation in fish (Annex IX) by either

- In vitro test OECD TG 319A/B (i.e., intrinsic clearance in rainbow trout hepatocytes) and in vitro–in vivo extrapolation (IVIVE) for estimation of kinetic BCF

or

- Bioaccumulation in invertebrates (e.g., Hyalella azteca bioconcentration test)

Increase information requirements – endocrine disruptors

- **Consideration to base in vivo follow up on weight-of-evidence approach, including for low tonnage substances**

  Triggers/waivers under discussion

- **Additional requirements for ED-identification human health:**
  - Uterotrophic Bioassay in Rodents (OECD TG 440)
  - Hershberger Bioassay in Rats (OECD TG 441)

- **Additional requirements for ED-identification environment:**
  - Amphibian Metamorphosis Assay (OECD TG 231)
  - Fish Sexual Development Test (OECD TG 234)
  - Medaka Ext. One-Generation Reproduction Test (OECD TG 240)
  - Larval Amphibian Growth and Development Assay (OECD TG 241)

Potential deletions of information requirements

To update to scientific progress and balance the additional low tonnage & ED requirements, the following are proposed to be deleted:

- acute oral toxicity in rats (Annex VII)
- acute dermal & inhalation toxicity in rats (Annex VIII)
- skin corrosion/irritation (Annex VIII)
- serious eye damage/eye irritation (Annex VIII)
- assessment toxicokinetic behaviour derived from the relevant available information (Annex VIII)
- further studies beyond the 90-day study (Annex IX column 2)
- long-term repeated toxicity study (≥ 12 months) (Annex X)
- pre-natal developmental toxicity study 2nd species (Annex X / trigger in Annex IX)
- carcinogenicity study (Annex X)?

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Input of CARACAL to proposed changes:

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Concerns raised CARACAL – high level

Member States & health protection NGOs

- Reluctance or objection to replacing in vivo methods
- OECD standardisation of NAMs required
- Lack of confidence in NAM even if high predictivity demonstrated
  (e.g., CATMoS method on > 48 000 chemicals: 96% predictions are overlapping or more conservative than in vivo LD50.)
- Can't change REACH before UN GHS criteria changed
- NAMs can indicate presence but not absence of hazard

Animal welfare NGOs, Industry

- Support the NAMs proposed to be introduced
- Support proposed deletions of in vivo tests & suggest WoE approaches to cover endpoint
- Do not support (all) the in vivo tests proposed for ED-identification

COM considerations

- **Change of regulatory requirements toward NAMs is the strongest driver for their use**:

  - decrease of in vivo irritation and sensitization tests after REACH changes in 2016/2017
  - decrease in vivo pyrogenicity testing only since its deletion in the EU pharmacopoeia is announced – despite in vitro assay listed in EU Ph since 2010

- **Have to start somewhere** – some gaps in applicability domain might be addressed or other solutions found if the NAM method is mandated

- Methods can be **sufficiently standardized** even if there is no OECD TG yet

- **Laboratory capacity for NAM-assays will increase** as soon as they become a regulatory requirement

- **Adaptations for a NAM SIR will remain possible**, could include in vivo as really last resort (with testing proposal or specific argumentation in Evaluation decision)

Changes to Annex XI

- Dual ambition:
  1) **incentivize (more) use of (more) NAMs** for adaptations
  2) **increase legal clarity what the adaptation needs to provide**
- Describe how an adaptation can provide an equivalent predictive capacity to the information that would be obtained from the study normally required
  → more guidance to be developed per endpoint
- Spell out what characterizes a valid in vitro method or defined approach
- Results shall still be adequate for the purpose of classification and risk assessment

  (→ need to agree how to classify based on NAM-information)

Beyond the REACH revision 2023: Roadmap for chemicals legislation

- Commission and ECHA are working **towards a Roadmap** for conducting **chemical safety assessment** without animal testing

- Looking forward to collaboratively identify critical needs necessary to **transit to an animal-free system**

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Thank you

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