How to ensure the safe use of nanomaterials under REACH – Part II: Current best practices for human health and environmental hazard assessment for nanomaterials

Outcome of the 2nd GAARN meeting held in Helsinki on 21-22 January 2013

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Outline

- Objectives of second GAARN meeting
- Summary
- Best practices
- Conclusion

1. Objectives of second GAARN meeting

- Best practices and recommendations on how to fill potential information gaps
- Assessing the safety of nanomaterials under the REACH Regulation
  - Human health and environmental hazards
- Increase confidence and mutual understanding among stakeholders
- Three GAARN meetings planned

2. Summary

- Three registration dossiers identifying nanoforms or nanomaterials
- Exchange of questions between ECHA and lead registrants prior to the meeting
- Experts participating
  - Member States
  - European Commission
  - ECHA
  - Two industry organisations
  - Three lead registrants

3. Best practices

- 3.1. General considerations

- Best practices based on the second GAARN meeting published on ECHA nanomaterials web page:
- http://echa.europa.eu/chemicals-in-our-life/nanomaterials

- 3.1.1 Use of non-testing data

- Supported for nanomaterials
- A solid scientific justification should be provided
- Insufficient to justify read-across based only on the chemical composition of a nanomaterial
  - aspect ratio, shape, form, solubility, surface area, charge, surface treatment, etc.
- A basis for grouping should be established using the similarity rules specified in Annex XI of REACH.

- 3.1.2 In vitro testing

- Despite their current limitations, in vitro methods can be useful as a supportive tool for in vivo testing
- Many in vitro tests may need to be adapted before they can be applied directly for hazard assessment
  - appropriate sample preparation
  - adequate controls defined to monitor possible interferences

- 3.1.3 Reliability and use of existing data

- Peer-reviewed scientific studies should be considered and included in IUCLID dossier
  - to build multiple lines of evidence (e.g. Annex XI)
  - sufficient and unambiguous information on the physicochemical properties of the nanoform are reported in the peer-reviewed studies to make them useful for registration purposes under REACH
- The methodology used for sample preparation and dosimetry of exposure systems should also be well defined and reported
- Extensive literature reviews provide a good basis for determining the relevance of in vivo studies to be performed

- 3.1.4 Surface treated nanomaterials

- Information on surface treatment to be reported in registration dossier
  - physicochemical information on the hazard properties of each form
  - essential as surface modifications may affect the toxicokinetics of nanomaterials
- Coated and uncoated nanomaterials should have separate IUCLID endpoint study records for the different hazard endpoints
- If an adaptation to the REACH information requirement is used, the registrant should ensure that it meets the requirements in Annex XI

3. Best practices

- 3.2. Specific considerations

- 3.2.1 Bioavailability: toxicokinetics

- Encouraged for grouping substances in relation to read-across
  - Absence of toxic effects cannot be explained only on the basis of physicochemical properties and adequate and supportive data on toxicokinetics are crucial
  - Use of toxicokinetic data useful when extrapolating from in vitro to in vivo situations
- If evidence of systemic translocation of nanoparticles,
  - further investigations on absorption, distribution, metabolism and excretion parameters should take special consideration
- Data on toxicokinetics useful for determining the testing strategies for environmental endpoints

- 3.2.2 Bacterial mutation assays

- The Ames test may not allow a robust evaluation of nano(particle) mutagenicity
- Bacterial mutation assays should be used in conjunction with a range of mammalian cell gene mutation tests

- 3.2.3 Sample preparation

- Registrants provide a detailed description of the sample preparation for (eco)toxicological assays in the relevant hazard endpoints (IUCLID)
- The OECD guidance on sample preparation and dosimetry (2012)

- 3.2.4 Environmental parameters

- Dissolved organic material , ionic strength, pH, etc. play an important role in stabilising nanomaterials, and thus can affect their bioavailability
- Bioavailability and thus hazard assessment of other chemical substances is also influenced by many of the above-mentioned parameters
- In the best scenario, prior work investigating the effects of these conditions on the stability and behaviour of nanoforms could help select the most adequate experimental design

- 3.2.5 Dispersing agents

- Use should be avoided for sample preparation for testing purposes
- If unavoidable to stabilise the dispersion, information regarding the concentration used and structural formula has to be provided in the relevant hazard endpoints (IUCLID)
- Use of dispersing agents may modify the behaviour, fate and bioavailability of the nanomaterial
  - appropriate controls should be documented in the study report, and a careful interpretation of the test results should be undertaken

- 3.2.6 Solubility and dispersion

- For in vivo and in vitro studies, exposure or dosing should be done with dispersed nanomateirals
- Special attention to the agglomeration/aggregation behaviour, and the insoluble/partially-soluble nature of nanomaterials
- Solubility studies are relevant to investigate the nano-effect and provide mass comparisons, and should be conducted mimicking the test exposure conditions
- Results should be reported at the study endpoints (IUCLID)

- 3.2.7 Test selection and design

- The half-life of nanoforms in suspension is often dependent on the initial loading concentration, with higher concentrations leading to faster precipitation rates
- High concentrations of nanoforms may impair the swimming ability of small invertebrates (e.g. daphnids)

- 3.2.7 Test selection and design

- For ecotoxicological endpoints, long-term studies are highly recommended for substances that show low toxicity in acute studies
- Most hazard assessments derived from available toxicological data from published peer-reviewed studies relate to short-term studies, whereas long-term studies are scarce
  - Given that the mode of action of nanoforms is yet to be properly characterised, carefully designed long-term studies might be of more relevance for an appropriate hazard identification

- 3.2.8 Relevant endpoints for ecotoxicity testing

- R.7 ECHA Guidance was recently updated with appendices containing recommendations for nanomaterials
- Aims to provide the registrants with advice on how link to identify potential hazards based on the latest scientific developments on the field of nanotoxicology
- In principle, the standard biological endpoints used in regulatory hazard assessment remain appropriate for nanomaterials in the context of supporting data for environmental risk assessment

- 3.2.9 Detection in the solid matrix/porous media

- Characterisation and concentrations of nanomaterials should be monitored prior and if possible during and/or at the end of the test (ECHA Guidance Appendix to R.7b)
- Detecting and quantifying nanomaterials from porous media e.g. soil or sediments is challenging
- Current scientific techniques allow to address this challenge through labelling of the nanomaterial (e.g., isotopic labelling)
  - Well-characterised nanomaterials delivered to soil and sediment systems in the form of water-based dispersions or mixed as dry material
  - If the nanomaterial is introduced and homogenised directly in solid or sediment media, care should be taken in homogenisation so that the test material is not unintentionally damaged

4. Conclusions (1)

- The scope of the registration dossier should be clearly identified, in line with the current nanomaterial definition (2011/696/EU)

- The provisions that need to be fulfilled for the registration of any chemical substance under REACH also apply to nanomaterials

- The use of grouping/read-across approach between different (forms of a substance should be adequately justified and documented

4. Conclusions (2)

- The registration dossier should contain a comprehensive physicochemical characterisation of the registered nanoforms
  - Read-across approach or use of existing data (e.g. weight of evidence) possible only when well-characterised nanoforms are reported in the dossier
  - Toxicokinetics data might also be considered
- Most standard biological endpoints used in regulatory hazard assessment remain appropriate for nanomaterials
  - Adaptations on sample preparation and dosimetry are foreseen for most of the tests
  - Parameters such as particle solubility and stability in the test media are essential parameters

4. Conclusions (3)

- Lack of short-term toxicity should encourage to investigate the potential sub-lethal and long-term effects
  - Might be more relevant for appropriate hazard identification
  - Unknown specific mode of action of most nanomaterials
  - Widespread exposure considerations
  - Difficulties in sample preparation and dosimetry of high concentrated exposure suspensions

5. References

- Report from second GAARN - best practices for REACH registrants:
- http://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_en.pdf

- ECHA nanomaterials web page:
- http://echa.europa.eu/chemicals-in-our-life/nanomaterials

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Thank you