Cefic on the amendments of the REACH Annexes in Commission Regulation (EU) 2018/1881 amending REACH to address nanoforms of substances

On December 4th, 2018 REACH Annexes I, III, VI, VII, VIII, IX, X, XI and XII were amended to address nanoforms. After a thorough analysis of the amendments, Cefic would like to highlight the following identified issues and potential solutions towards the 1st of January 2020 deadline.

Concept of nanoform (Annex VI introduction)

- The term nanoform in Annex VI, is defined as *'a form of a natural or manufactured substance containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm, including also by derogation fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm'*.
- Cefic considers it necessary to indicate, in unambiguous terms, that a nanoform can comprise of several product grades of the same substance if they fit appropriately in the phys-chem parameters for nanoforms defined in section 2.4 of Annex VI. Other interpretations might lead to the understanding that information at the single commercial product grade level can be required. REACH is a substance based regulation and therefore requiring information based on individual market products would create an unlevel playing field for nanomaterials.

Concept of 'set of similar nanoforms' (Annex VI introduction):

- Cefic agrees on the need for the inclusion of the concept of a "set of similar nanoforms" in the REACH Annexes to facilitate risk assessment and demonstration of safety. In our view, a "set of similar nanoforms" can be included in IUCLID by using the "assessment entity" function.
- A 'set of similar nanoforms' includes several nanoforms. The characterisation parameters from Annex VI paragraphs 2.4.2 to 2.4.5 should be given per set of similar nanoforms and not per nanoform included in the set to define their boundaries. That would create an unproportionate burden for the registration of substances containing nanoforms, without any added value for the objectives of the REACH regulation.
- Annex VI indicates that *'A justification shall be provided to demonstrate that a variation within these boundaries does not affect the hazard assessment, exposure assessment and risk assessment of the similar nanoforms in the set.'* The justification required should be proportionate, i.e. the testing requirements should be limited in order to maintain the purpose of the registration of the nanoforms as a set – i.e. to demonstrate safety.

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Tonnage requirements

- Volume-dependent information requirements under REACH are related to the registered volume of the substance in all forms covered by the registration. Where several forms of a substance are covered in one REACH registration dossier, this may result in a huge number of new data requirements. Therefore, for reasons of workability, proportionality, animal welfare and cost-efficiency, formation of large groups ('sets of similar nanoforms') with similar characteristics should be supported and accepted. In addition, the formation of different 'sets of similar nanoforms' for different endpoints should be encouraged. This is especially important in terms of innovation, which could be the preparation of a new slightly modified nanoform of an existing substance.

Exposure as a grouping tool

- Exposure as a tool for grouping should be further investigated. Cefic believes some of the concerns authorities and civil society have raised could be addressed via this route. We would like to suggest including this topic for the future discussion on the ECHA Guidance.

Contract Research Organization (CRO) readiness

- Because of the revision of the TGs and guidance documents the CROs need to adapt their protocols and train to ensure the test are conducted correctly. With the actual timelines, it will be very challenging to find enough CROs already working with the new TGs fully implemented. That can potentially further delay the availability of the data for registration.

Dissemination of information and downstream users obligations

- The amendments of the Annexes add complexity as any modification to the particles done down the supply chain should also be covered by the registration dossier. To make it workable we suggest to incorporate information on the brief profiles at the 'set of similar nanoforms' level. It would simplify the dissemination of information relevant for the downstream users.
- Moreover guidance would be needed for the downstream users to be familiar with their obligations and responsibilities.

Toxicokinetics

- The ECHA guidance for human health information requirements for nanomaterials indicates that:

  "The standard information requirements defined by the REACH regulation can give useful information to help make a judgement about the possible toxicokinetics of nanomaterials (See Section R.7.12.2.1).

  Information on the possible behavior of the nanomaterials can be supplemented with in vitro and in silico predictions based on physicochemical and other data. This information may be used in grouping of nanomaterials to assist in the read-across of exposure and hazard characteristics, thereby reducing the total number of tests required."

- Cefic agrees with that statement, other required endpoints should be accepted as sources of toxicokinetic data. A full toxicokinetic analysis with no added value should be avoided.

Adequate justification

- Throughout the Annexes the term Adequate justification is repeated. Clear examples of what adequate justification means should be included in the guidance. The information required for the justification should not defeat the purpose of grouping forms and prevent the use of read across.

Metrics conversion

- In Annex I, paragraph 0.11 bis, is stated that *'0.11.bis When nanoforms are covered by the chemical safety assessment, an appropriate metric for the assessment and presentation of the results in steps 1-6 of the chemical safety assessment under 0.6.1 and 0.6.2 shall be considered, with the justification included in the chemical safety report and summarised in the safety data sheet. A multiple metric presentation, including mass metric information, is preferable. When possible, a method for reciprocal conversion shall be indicated.'*
- The rationale behind this request is not clear, since the conversion between metrics increases the uncertainty. Hence the usefulness of providing multiple metrics is unclear.

Test guidelines/Guidance documents under development

- For those endpoints where the test guidelines and guidance documents are still under development, e.g. degradation, water solubility, dissolution rate, an interim solution should be accepted. We suggest to either use existing information, or, indicate in the dossier 'Test proposed, data not available yet'. Performing a test if the standard test is under development should be discouraged.
- Cefic wants to ask for ECHA to include in the guidance a list of accredited methods that are available and accepted.

Solubility

- To determine if a substance is soluble or not the OECD TG 105 should be accepted at the valid method. Substance with solubility of 100mg/L should be considered soluble, this should be included in the guidance documents. This would align with the German Announcement 527 where it is written: "The solubility in water is pragmatically used in this Announcement as a criterion to assess biopersistence. For the purposes of this Announcement, nanomaterials with a solubility in water of less than 100 mg/l are practically insoluble and therefore bio-persistent. As a consequence, nanomaterials with a water solubility above 100 mg/l are regarded as soluble. When findings are available on the solubility of nanomaterials in biological media, these shall be primarily used for the assessment of biopersistence."

QSAR limitations

- The use of QSAR methodologies is limited for nanomaterials at this time, this should be clearly recognised and considered in the development of the guidance documents for the update of the dossiers.

log K_{ow}

- Recent publications[1] suggest that the log Kow is not adequate for nanomaterials.

Dustiness – test guidelines not adequate for nanomaterials

- Dustiness is not an intrinsic property of the material. It depends on the conditions of exposure.
- Moreover, the OECD standardised method is still under development for nanomaterials. As previously mentioned the use of non standardised methods should be discouraged.

Inhalation route

- Inhalation may be the more relevant route of exposure for nanomaterials compared to oral application. However, the acute inhalation toxicity study (OECD TG 403 and TG436) is not adequate for nanomaterials as materials of low intrinsic toxicity have to be tested at the limit dose of 5,000 mg/m^3. Here, deaths of animals are to be expected because this high nanoparticle concentration in the air will congest the trachea of the exposed animals, which will die due to a mechanical suffocation effect instead of the intrinsic toxicity of the substance. We propose to reconsider the limit dose for the results to be substance relevant.

Short term toxicity testing in invertebrates

- We believe clarification is needed on the sentence that reads *'Moreover, for nanoforms highly insolubility in water alone cannot serve as justification for waiving the test.'* We propose the following addition 'if a colloidal resuspension could be presumed for the nanoforms'.
- Clear criteria on what high insolubility means should be included in the guidance.

Additional phys-chem parameters

- Cefic believes that a routine request from authorities for additional phys-chem parameters cannot be accepted; pragmatism should be the rule. A request for additional phys-chem information should be well justified. Cefic would like to encourage an open dialogue with the registrants before additional information is required.

[1] An Assessment of Applicability of Existing Approaches to Predicting the Bioaccumulation of Conventional Substances in Nanomaterials, https://repository.nwu.ac.za/bitstream/handle/10394/31697/An_assessment.pdf?sequence=1

Indirect genotoxicity

- Cefic firmly believes that the interpretation that indirect genotoxicity is referring to secondary genotoxicity is incorrect. This is not a nanospecific property, to require it for nanomaterials creates an unlevel playing field.

Degradation

- *"For nanoforms that are not soluble, nor have high dissolution rate, such test(s) shall consider morphological transformation (e.g. irreversible changes in particle size, shape and surface properties, loss of coating), chemical transformation (e.g. oxidation, reduction) and other abiotic degradation (e.g. photolysis)."*
- Degradation can only be measured qualitatively, a quantitative analysis is not possible, the requirements for this endpoint need to be clarified in guidance.

January 2020 deadline

- On 1 January 2020 the nanospecific amendments of REACH Annexes enter into force. Besides the issues addressed above neither the Guidance on Registration and substance identification nor the Guidance on Information requirements and chemical safety assessment have been revised to reflect the nanospecific REACH Annexes amendments, and only a first draft on the nanospecific Appendix on the Guidance on Registration and substance identification has been submitted to an expert group. Also for a number of tests OECD test guidelines are still missing. This makes it impossible for industry to implement the REACH Annexes amendments in their registration dossiers already on 1 January 2020 as crucial guidance is missing. ECHA and the Commission must find a solution that this does not lead to dossiers being marked non-compliant or incomplete.

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About Cefic
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