Nanomaterials and REACH – What Do I Have to Do Differently?

Part 3: Adjustments to toxicological, eco-toxicological and physico-chemical testing for nanomaterials

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No toxicological mechanisms that are specific to nanomaterials as a whole have been identified so it is felt that the endpoints required for other substances under REACH are largely also applicable to nanomaterials. However, the unique properties of nanomaterials must be taken into account when designing a study. The update to REACH states which endpoints need to be satisfied using different protocols to those usually used for other forms of a substance. There is ongoing work by the OECD and ISO to develop standardised testing protocols and these should always be used when available but an exhaustive selection may not be fully developed to meet the dossier update deadline of Jan 2020.

Particle Characteristics that impact on the hazard assessment of nanomaterials

It is important that the endpoint studies are performed on the substance in the form that it is placed on the market and it is important to characterise the substance tested. However, it might not be vital to have a dispersion of the primary particles when describing the sample for the endpoint study. Instead, the degree of agglomeration/aggregation and size distribution of these structures will be important, especially when trying the justify membership of a set of similar nanoforms or a read-across. These particle characteristics can have an important impact on the hazard of the substance.

The analytical strategy for assessing whether a substance is a nanomaterial or not is described in an earlier white paper in this series.

Table 1: Physico-chemical parameters that may affect the toxicology of a nanomaterial.

Parameter	Example
Chemical composition	Different substances with identical physical shapes show significantly different toxicological profiles. Some nanomaterials are believed to cause toxic effects by the release of ionic forms of the substance (e.g. silver nanoparticles)
Particle size	As the dimensions of a particle decrease, its surface area to volume ratio increases. As the chemistry of a solid usually occurs on its surface, particle size reduction can lead to increased reactivity. In addition, small particles may be able to cross biological membranes that larger ones cannot.
Particle shape	Acicular particles may be able to penetrate some areas of the body but then are able to frustrate the natural mechanisms that the body has to remove foreign bodies. This can lead to chronic inflammation and tumour formation.
Zeta potential	The charge on the surface of a particle may influence its tendency to agglomerate and its surface reactivity.
Agglomeration/ aggregation	If nanoforms agglomerate or aggregate, their free surface area can be reduced and they may not be able to reach the organs that primary particles can.
Surface treatment	The surface of a particle is where its chemistry occurs, so changes to the surface can change the biological and chemical activity of a substance.

Therefore, it is essential to measure the relevant parameters in order to be able to properly control the risk associated with the nanomaterial and accordingly, the update to REACH requires that registrants assess each variable.

Physico-chemical testing

Many of the physico-chemical properties required for REACH are used in modelling programmes used for workplace or environmental exposure estimation. Commonly used models for chemicals assume the creation of a thermodynamic equilibrium of the substance between different environmental compartments. The environmental fate of nanomaterials is governed by kinetic rather than thermodynamic factors meaning that alternative parameters need to be measured for some endpoints. For example, partition coefficient is not relevant to

nanomaterials and should be replaced by an assessment of agglomeration in different media and bioaccumulation. Rate of dissolution is required as well as solubility.

More detailed discussion can be found at:
https://echa.europa.eu/documents/10162/13564/appendix_4_nano_registration_committees_en.pdf/1abb12d1-88a2-b386-0907-c67d05105378

Toxicological testing

In order to allow read-across between different nanoforms, the sample tested must be very well characterised. The absence of good characterisation in historic research means that care must be taken if these studies are used in a hazard assessment. Perhaps the most important change to the endpoint testing requirement for nanomaterials is that inhalation should be regarded as the key route of exposure instead of oral exposure. This is of particular significance to substances in the 1 – 10 tonne band, where only one route of exposure is required for toxicity testing, as exposure by inhalation testing is often more expensive than its oral equivalent. In addition, the protocol used must be designed to ensure false negatives or positives are avoided. Particles cannot cross bacterial cell walls meaning that the Ames test should be replaced by a mammalian cell mutagenicity study.

More details can be found at
https://echa.europa.eu/documents/10162/22334053/draft_for_committees_app_r7-1_r7-2_en.pdf/e0efc82b-fed8-f80e-692b-408b75fbae2d

Ecotoxicological testing

As with toxicological studies, the nanoform in question should be well described for ecotoxicological studies and it may be appropriate to analyse both before and during testing to highlight any changes in nanoform. Nanoparticles are small enough to be taken up by aquatic organisms meaning that they can exert an adverse effect even when undissolved. This means that the usual waivers for some aquatic toxicity studies do not apply to nanomaterials.

More detailed discussion can be found at:

https://echa.europa.eu/documents/10162/22334053/draft_appendix_r7a_caracal_en.pdf/1233776b-a684-c8e3-a5fd-7f279e7200b2

https://echa.europa.eu/documents/10162/22334053/draft_appendix_r7b_caracal_en.pdf/ca2de51a-3068-2d4c-0eeb-a449df41bd2d

https://echa.europa.eu/documents/10162/22334053/draft_appendix_r7c_caracal_en.pdf/f6af9bb9-2d23-9ba9-abc3-430d10ddba98

The hazard assessment of nanomaterials should be done across the whole lifecycle, so the choice of the sample tested is crucial to interpreting the results. The current testing requirements for a bulk substance are deemed adequate for nanomaterials under REACH with some modifications. These are being continuously developed and are likely to appear in guidance documents as they are revised.

Read-across and grouping

The revised regulation requires a full set of endpoint data for each set of similar nanoforms. This could be prohibitively expensive if all these endpoints had to be satisfied by commissioning new studies. Therefore, it will be crucial to use scientifically justified grouping and read-across approaches between different nanoforms or between nano and bulk forms. For example, it has been suggested that all high aspect ratio, low solubility nanomaterials might all be regarded as toxic by inhalation as they would all trigger frustrated phagocytosis and inflammation. If the nanomaterial is highly soluble, read-across to the bulk form could be justified. The same approaches will be needed to define and justify the limits of a similar set of nanoforms. There are a number of EU funded projects investigating approaches to grouping and read-across for nanomaterials, such as GRACIOUS (https://www.h2020gracious.eu/)

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