Using read-across and categories to improve safety of nanomaterials

INTERVIEWS BY TIIU BRÄUTIGAM

Read-across and category approaches are used to predict properties of substances for which there is not enough experimental data. This is a pragmatic way to bridge data gaps to characterise the hazards of nanomaterials. ECHA Newsletter spoke with *Dr Wim de Jong* and *Dr Robert Landsiedel* about recent developments in this field.

Dr Wim de Jong.

Dr Robert Landsiedel.

What are the main developments regarding the risk assessment of nanomaterials?

Robert Landsiedel, BASF, Germany: We realised a decade ago that nanotechnology would offer great opportunities for improving our lives, but might also bear risks for human health. Since then, researchers have been studying the toxic effects and underlying mechanisms of nanomaterials.

We now have a good idea of which nanomaterial applications pose a risk to human health and which ones can be used safely. In fact, with industrial nanomaterials, few adverse systemic effects have been reported. Inhaling dust particles is the main route of exposure. There are no toxic effects that are unique to all nanomaterials. In this sense, the nano-specific health effects anticipated years ago have not been confirmed by research.

So, there is no general nanotoxicology but different nanomaterials have different toxic effects. These need to be identified to ensure their safe use. Nanomaterials are used in various modifications and compositions. It is not possible to run studies with all the potential modifications. Instead, we need to define various groups of particles, according to their potential to cause adverse effects to humans.

Wim de Jong, National Institute for Public Health and the Environment, the Netherlands: I largely agree with Mr Landsiedel that no nano-specific health effects have been identified in the last years, but we need to learn more about particle toxicology. Up to 10-15 years ago, particle toxicology was mainly inhalation toxicology, so we have a lot of knowledge from this area. Inhalation is also one of the most identified health risks from nanomaterials. Now new products are being developed which contain nanoparticles, for example, sunscreens. Here we see other routes of exposure beyond inhalation. So, we are moving from inhalation toxicology to more general toxicology and here we see that nanoparticles behave differently to soluble chemicals.

Both industry and regulators want to develop grouping approaches. Based on the information provided by industry, regulators look at the characteristics of safe materials and the criteria for safe use of a particle. Knowledge about the migration and persistence of nanomaterials is also becoming more important and triggers concerns.

How do read-across and category approaches relate to this development? Why are they important?

Robert Landsiedel: Nanomaterials are typically embedded in a product or used on its surface. To become toxicologically relevant, they need to be dispersed or released from the product.

It is neither possible to test each different nanomaterial exposure for all of its toxicological properties, nor do we have a full understanding of how the material properties of nanomaterials may cause adverse health outcomes. As such, classical QSAR computer modelling approaches are not yet capable of providing a sufficient grouping concept.

We propose to use a multi-perspective approach: rather than taking 'the long shot' from material properties to adverse outcomes, we should also look at the steps in between: the life-cycle of the nanomaterial; the exposure; uptake; distribution; biophysical interactions; as well as cellular and organ responses, to understand which nanomaterials could be grouped to-

gether with regard to their adverse health effects.

Wim de Jong: In view of the expected development of new or modified nanomaterials, there is a need for read-across and grouping. To evaluate nanoparticle UV filters in sunscreens, first steps have been made in grouping and read across. These approaches were used to evaluate the same nanomaterial which was produced by different manufacturers. However, for unknown particles, we still have to apply other methods, such as high throughput screening, which gives more information on nanomaterials in a relatively short time. We can also evaluate modes of action or modes of activity. These are mainly used for prioritising nanomaterials, to find out the most toxic ones where we need more information.

Eventually, this information can be used for grouping low-toxic potential materials and high-toxic potential ones, where more information and a more complete risk assessment are needed. However, this is still based on animal testing.

We are not yet there in terms of replacing all animal tests, but there are encouraging developments. For example, there are European projects that use high throughput screening to identify modes of action for toxicity. Common mechanisms of action might be a first step to identify specific groups of nanomaterials.

Which common approaches for read-across and categories of conventional chemicals can be applied to nanomaterials? Where do you see the main challenges?

Robert Landsiedel: We already have a lot of tools at hand for grouping, read-across, waiving and categories. The ECETOC taskforce on nanomaterials recently suggested a framework to pull together different concepts in a multi-perspective approach. The idea is not to restrict grouping to only one aspect, but to use and combine all the different tools for grouping that are already available.

While the framework for a multi-perspective grouping is already within reach, a major challenge will be the design of a decision-tree and defining the criteria for it. Some criteria for grouping are obvious to apply, such as bio-kinetics, bio-physical interactions or early biological effects, while others, such as long-term effects, are currently being investigated.

The definition of groups and sub-groups will require reference materials and case studies of nanomaterial examples. The multi-perspective grouping offers a flexible decision-making framework, which can be used and further developed at the same time.

Another challenge will be the generation of data to assign nanomaterials to groups. A substantial amount of data is already available from the physico-chemical characterisation of the materials and from short-term inhalation studies.

Wim de Jong: We know that a nanomaterial behaves differently in terms of reactivity, because it is made specifically to be, for example, a more efficient catalytic agent or colouring agent. There is a reason why the nanomaterial has been produced. Why would you otherwise use a nanomaterial if the bulk material had the same properties?

There are limits to extrapolation, for example, based on information about the toxicity of the chemical structure. Ultimately, however, you also need nano-specific information. Characterisation is important to identify the nanomaterial.

However, to make a decision on grouping, a list of characteristics is not enough. You also need practical information on different assays. It is still difficult to come to a grouping which would be based on physico-chemical parameters on its own.

We see also the use of principal component analysis, where a set of characteristics are combined to come to an integrated picture. These are very complicated analyses. Here, some kind of grouping is possible, but it is not yet correlated with toxicity.

There is one specific challenge for the near future. Even if you can group some nanomaterials based on the principle component analysis, you want to know what it means for that particular group. How does that group behave in terms of toxicity or adverse effects?

Have the read-across and category approaches reduced the need for animal testing?

Robert Landsiedel: Yes they have. At BASF, we use categories in the risk assessment of applications of nanomaterials. As a result, we do not subject each nanomaterial in each modification to a fixed list of animal studies. Instead, we perform the studies needed for the risk assessment of the nanomaterial in its own application. With this information, we select those materials with sufficiently low hazard for a given application and applications with adequately low exposure.

Industry and authorities share the same ultimate goal of reducing animal testing, but we are not there yet. Animal data will still be needed on some materials. Eventually, we will be able to predict adverse outcome from material properties. Until then, we can do risk assessments and work on grouping based on exposure, uptake, distribution, biophysical interactions as well as cellular and organ responses. Several of these data can already be obtained without animal studies; and hopefully more or all of them in the future.

Wim de Jong: Industry is working on a multitude of nanomaterials now. They need to make a choice about which materials fulfil the information requirements and are safe for the market before the dossiers come to the regulators. So, in a pre-clinical or pre-marketing situation, there are many modifications possible on nanomaterials. High-throughput screening and read-across can be used on the preselection of those materials that industry wants to continue developing. However, for the nanomaterial that is finally selected, regulators will not yet rely on grouping and will still need animal data for the risk assessment.

All governments want to reduce animal testing. Categories and grouping is one of the ways to do it, although we still need more information before these can be applied for nanomaterials.

Further information:

Nano terminology – in 23 languages
http://echa.cdt.europa.eu/Search-ByQueryEdit.do

Nanomaterials
http://echa.europa.eu/regulations/nanomaterials

Nanotechnology
http://echa.europa.eu/chemicals-in-our-life/hot-scientific-topics/nanotechnology

Scientific Workshop – Regulatory Challenges in Risk Assessment of Nanomaterials
http://echa.europa.eu/en/view-article/-/journal_content/title/topical-scientific-workshop-regulatory-challenges-in-risk-assessment-of-nanomaterials

DID YOU KNOW?

Dr de Jong and Dr Landsiedel participated in ECHA's workshop on nanomaterials in October 2014. The workshop brought together almost 200 experts in the risk assessment of nanomaterials. They discussed scientific principles and guidelines for assessing human health and environmental risks of chemical substances in nanoform. The workshop also provided a platform for academia and regulators to address how the long term challenges from the regulatory perspective can be reflected in research topics on nanomaterials.

Your feedback improves Biocides tool

TEXT BY LIVIA BRIESE AND PÄIVI JOKINIEMI

The new release of R4BP 3 was published in early December. It is a major upgrade that comes with many new features making it easier for applicants to submit their biocides applications. The improvements have been developed based on feedback received from users. Read what you can do with the new features and learn about the new editor to create summaries of product characteristics.

R4BP 3 is the single point of entry when working on biocides applications. It allows you to securely interact with authorities and is well-protected data archive. There are 27 additional processes which are defined in the Biocidal Products Regulation (BPR) that have been included in this latest version of R4BP 3. You can now do more with this one single tool.

Presenting and connecting data in R4BP 3 is improved. For example, links between granted authorisations are visible, clearly improving the overview of your products.

With the new release all national authorisations for biocidal products and ongoing applications are now in R4BP 3. From 3 December 2014, only one system has been in place: R4BP 3. This means that applications for national authorisation of biocidal products which started in R4BP2 will be processed in R4BP 3.

Easier mutual recognition in parallel

If you need an authorisation to use your product in more than one European country, you no longer have to submit multiple applications separately. Once you have applied for your initial product authorisation, you can choose all the countries where you want to apply for mutual recognition in parallel and the application will be submitted automatically to all of your chosen countries.

Nominate, delegate and transfer rights

The new release also allows you to nominate, delegate and transfer rights on your products to another