The dose makes the poison

The detailed characterization of the materials is essential in all areas of nanotoxicology.

Fish, worms, rodents, algae, bacteria and cells. Carbon nanotubes, metal oxides and quantum dots. Choose a model system from the first list and a nanomaterial from the second, and chances are that you will be able to find two or more toxicology studies that report slightly different conclusions about the impact of the latter on the former. Twenty years of research has confirmed that nanoscale materials can display unexpected and unusual toxicity, but just how much have we learnt about the interactions between engineered nanomaterials and humans, animals and the environment?

The Society of Toxicology defines toxicology as "the study of the adverse effects of chemical, physical and biological agents on people, animals and the environment"[1], and the sheer diversity of nanotoxicology can be seen on a web page that contains links to all the articles that *Nature Nanotechnology* has published on the subject[2]. One characteristic of nanotoxicology is that materials that are not harmful in their bulk form may well be toxic on the nanoscale. Bulk gold, for example, is normally inert but gold nanoparticles are anything but inert, which is why they are useful for applications such as medical imaging and drug delivery. However, nanoparticles are also more likely to react with cells and various biological components such as proteins, and to travel through organisms, which increases their chances of entering various organs and activating inflammatory and immunological responses[3].

In a typical toxicity test, cells or organisms are subjected to a dose of chemicals, and the response is measured over a period of time; the dose–response relationships obtained in these experiments are important because they are used for determining appropriate dosages for drugs and acceptable limits for exposure to pollutants. However, unlike the soluble chemicals tested in traditional toxicology studies, nanoparticles have shapes and surface areas, and they can diffuse, aggregate/agglomerate and sediment according to their size, density and physical and chemical properties in solution. This means that traditional *in vitro* assays may misrepresent the response and cellular-uptake data for nanoparticles, making the test results less comparable across particle types than for soluble chemicals[4]. On page 385 of this issue Xia and co-workers show that sedimentation of nanoparticles can influence how many nanoparticles are taken up by cells in an *in vitro* assay, and on page 332, Lison and Huaux discuss the different options for defining the relevant cellular dose for such tests.

> There are opportunities for computational scientists to work with toxicologists to design new assays.

Another issue in nanotoxicology is the impact of nanomaterials on the environment. Many toxicity studies, until now, have been done at much higher doses than is realistic[3] and they may exemplify Paracelsus's observation of "the dose makes the poison" — toxic substances are harmless in small doses and harmless substances are poisonous when over-consumed. Quantifying real-life occupational exposures and emissions of nanoparticles into the environment is a challenge; modelling studies that consider various release scenarios based on the life cycle of the nanomaterials and products that contain them have been presented, but to improve these models we require data on the industrial production of nanomaterials, the amounts released at different stages of the life cycle of the materials, and the form in which they are released[5].

The chemical and physical properties of nanoparticles have a strong influence on the way in which they interact with biological components or the environment at large, and also on the way they move, accumulate and clear in the body. For example, nanoparticles acquire a 'corona' of proteins when exposed to biological fluids, and this layer is thought to influence the way the cell 'sees' the nanoparticle[6]. It has also been shown that certain nanoparticles can induce proteins to unfold, leading to an inflammatory response[7]. Similarly, nanoparticles are coated with natural organic matter when they enter water, soil or sediment environments and this layer influences their reactivity, bioavailability and other transformations in the environment[8]. These dynamic interactions add complexity to the challenge of determining the biological outcome of nanoparticles.

Studying the influence of the various properties of nanomaterials, the dose, the exposure route and time, and identifying the right model systems is expensive and time consuming. High-throughput and computational approaches are on the horizon to rapidly screen and prioritize nanomaterials for toxicological tests and to develop causal relationships between material properties and biological behaviours[9]. Researchers have shown, for example, that the quantitative structure–activity relationship (a statistical model traditionally applied to chemicals) can predict the cytotoxicity of a small set of metal oxide nanoparticles[10]; there are also opportunities for computational scientists to develop appropriate structural parameters for describing nanomaterials and to work with toxicologists to design new assays[11].

For the field to progress, it is necessary for all papers to report detailed characterization of the materials used so that data from the toxicity studies can be properly interpreted, reproduced and compared by others[12]. And the big challenges in the coming years are to understand how physical and chemical properties of nanomaterials govern their interactions and responses, and to inform the public on the benefits and risks associated with the use of nanomaterials. ❐

References

1. http://www.toxicology.org/index.asp
2. www.nature.com/nnano/focus/nanotoxicology
3. Oberdörster, G. *J. Intern. Med.* **267,** 89–105 (2010).
4. Teeguarden, J. G. *et al. Toxicol. Sci.* **95,** 300–312 (2007).
5. Gottschalk, F. & Nowack, B. *J. Environ. Monitor.* **13,** 1145–1155 (2011).
6. Lynch, I. & Dawson, K. *Nano Today* **3,** 40–47 (Jan/Feb 2008).
7. Deng, Z. J. *et al. Nature Nanotech.* **6,** 39–44 (2010).
8. Aiken, G. R., Kim, H. H. & Ryan, J. N. *Environ. Sci. Technol.* **45,** 3196–3201 (2011).
9. Fourches, D., Pu, D. & Tropsha, A. *Comb. Chem. High T. Scr.* **14,** 217–225 (2011).
10. Puzyn, T. *et al. Nature Nanotech.* **6,** 175–178 (2011).
11. Burello, E. & Worth, A. *Nature Nanotech.* **6,** 138–139 (2011).
12. http://characterizationmatters.org/parameters/