Nanotoxicology and nanotechnology

Nanomaterials are commonly used in products within medicine, cosmetics, electronics, pesticides, semiconductors, microelectronics, energy storage and textiles to give new, improved features. However, concern has been raised that exactly these properties that make nanomaterials so unique and useful also could be coupled to unintentional effects on health or the environment. Thus it is important to obtain information about potential toxicity of nanomaterials to discover and prevent serious unwanted human effects. *The goal must be to realize the great opportunities and benefits of nanotechnology while at the same time minimizing the risk related to its applications.*

By now there is a great knowledge gap between nanotechnology and potential toxicity. If one search the PubMed database, which is a database comprising more than 20 million citations for biomedical literature (scientific papers and books), you will get 40651 hits for nanoparticles and only 2941 hits for nanoparticles and toxicity in combination. Thus research within the field of nanotoxicology is highly warranted. Norway has a well established platform when it comes to toxicological research, both within human toxicology and ecotoxicology, and many of these research groups are already involved in FP7 EU projects concerning nanoparticles and toxicity, and are part of excellent international networks. E.g. the health effects group at NILU is coordinating FP7 NanoTEST, and is a partner in FP7 NanoImpactNet, Qnano, NanOmega and NanoTOES, and is also together with the Norwegian Institute for Public Health involved in EEA grant PNRF-122 as well as NRC project SafeNano, the network of Norwegian institutions focussing on safety of nanomaterials. Hence, nanotoxicology should be included in the Norwegian strategy within nanotechnology. Nanotoxicology is a quite new topic and Norway has a potential to be a leading partner in the field by staking on the existing expertise within the scientific toxicological community and further development and strengthening of these environments.

Nanoparticles could potentially induce toxicity, primarily due to increased surface area coupled to augmented reactivity, enhanced mobility, and penetration of barriers. Although no health effects in humans have been discovered so far, experimental studies indicate that nanoparticles is coupled to adverse biological responses leading to toxicity (Oberdorster, 2010). For risk assessment of use of nanoparticles both intrinsic toxicity and exposure must be addressed. *Currently there is a knowledge gap between the accelerated development and use of nanomaterials on one hand and toxicity studies and prediction of health risks on the other hand.*

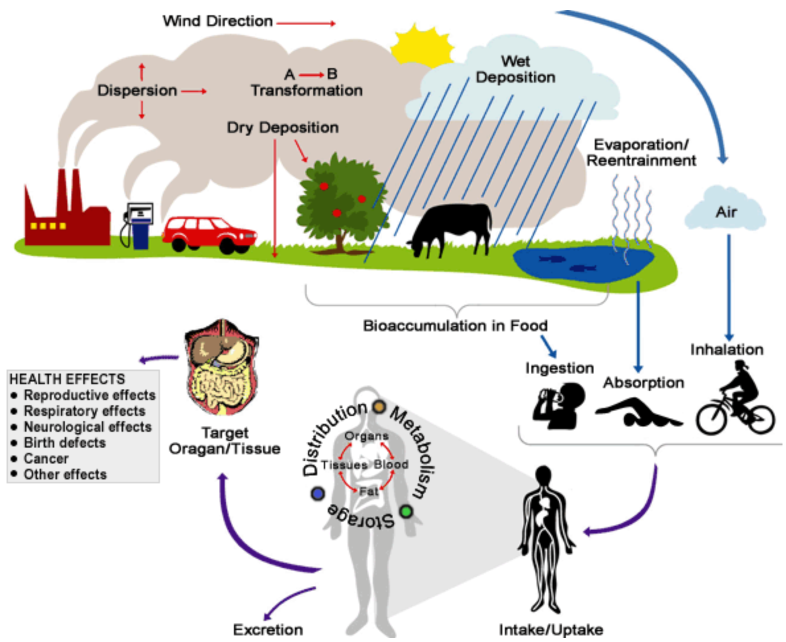
Human exposure routes for nanoparticles are by inhalation, dermal, oral intake or by injection (medical use). Traditionally the respiratory tract has been considered the target organ after inhalation of potential toxins, but after reaching systemic circulation nanoparticles have been found also in liver, lungs, heart, kidney, spleen and brain (Elder and Oberdorster, 2006). More research is needed for exploring what happens when nanoparticles comes into the blood circulation and which organs are affected. The diversity of nanoparticles will probably be reflected in dissimilar toxicity profiles and divergent exposure levels, and thus present challenges in toxicity assessment. The small size and the particle shape enables uptake into blood and lymph circulation and distribution to tissues in the body that normally are protected by barriers, such as the brain by penetration of the blood-brain-barrier (BBB). Nanoparticles have also been shown to cross the placenta and affect embryonic development. This rises concern about exposure of pregnant women and potential toxic effects on the fetus during development (Oberdorster et al., 2005).

The fact that nanoparticles can reach the brain after exposure by inhalation is a great advantage when it comes to nanomedicine and therapeutical treatment neurodegenerative disorders, as only 2 % of drugs are able to cross the BBB, but elicits on the other hand concern. Nanoparticles have been shown to translocate to the brain after inhalation, either by penetration of the blood-brain-barrier (BBB) or by transport via nerve endings in the nasal cavity (Oberdorster et al., 2004;Elder et al., 2006) (Bhaskar et al., 2010;Fernandes et al., 2010;Hanson and Frey, 2008;Sharma et al., 2009b;Sharma et al., 2009a;Trickler et al., 2010). However, the mechanisms underlying the translocation to the brain still remain to be elucidated. Axonal transport of biological nanoparticles, like viruses, was first revealed several decades ago. Already around 1930, Flexner *et al*. showed that polio viruses could enter monkey brains via the olfactory nerve from the nose (Flexner, 1933a;Flexner, 1933b;Flexner, 1935). The ability of nanoparticles to reach the brain and the central nervous system by intranasal delivery has been demonstrated also in humans with insulin to improve memory in both normal adults and patients with Alzheimer´s disease (Benedict et al., 2010;Born et al., 2002;Hanson and Frey, 2008). Consequently, uptake of nanoparticles into the brain and induction of neurodegeneration should be carefully explored.

Because of the diverse potential for nanoparticles, occupational and public exposure will increase dramatically in the years to come. The increasing use of nanoparticles in industrial applications will inevitably lead to release into the environment. In fact, millions of tonnes of nanomaterials are produced annually for commercial purposes. This makes nanotechnology a source of risk in spite of the great advantages coupled to the applications of nanomaterials. Thus effective analytical methods for exposure levels and screening tests for toxicity are important for performing risk assessment of nanoparticles. So far there is almost a complete lack of human exposure data when it comes to nanoparticles.

For performing risk assessment of use of nanoparticles, it is important to take into account life cycle of nanomaterials, including the following (see figure):

1) extent of use
2) environmental release during life span
3) persistence in body or environment
4) distribution in water, soil and air
5) intake routes and distribution in the body
6) potential toxicity towards cells, tissues and organs



Factors important for risk assessment analysis for nanoparticles

We would like to highlight some tasks within nanotoxicology which we think are important for Norway to contribute to:

1) Establish good test methods for toxicological testing of nanoparticles.
   An important task within nanotoxicology is to establish good test methods and guidelines for nanoparticles. Test methods set up for testing of toxic potential of particles is not necessarily suitable for nanoparticles due to changed properties due to their nanosize. So far many obstacles have been discovered, and further work on these ascpects is needed before consensus can be made for proper testing strategies of potential toxicity of nanoparticles. NILU is involved in the work with alternative testing strategies for the assessment of the toxicological profile of nanoparticles used in medical diagnostics within FP7 EU project NanoTEST.
2) Unravel the mechanisms underlying induction of toxicity of nanoparticles
3) Explore mechanisms for uptake of nanoparticles into organs and cells, especially translocation and uptake into the brain
4) Life cycle analysis and exposure estimations
5) Risk assessment strategy

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