Responsive development of nanotechnology

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Introduction
In its 2020 Strategy, the European Union (EU) highlights nanotechnology as one of the key enabling technologies (KET) promoting smart, sustainable and inclusive growth throughout the EU (1). Engineered nanomaterials (ENM) and nanotechnologies contribute considerably to the goals put forward in the EU Strategy. However, the safety of ENM has given rise to increasing concerns, not only for the public and regulators, but also for the industries using these materials. In fact, the EU Commission considers that uncertainties related to the safety of ENM represent a major obstacle to marketing and innovations based on these technologies (2). Hence, it is of the utmost importance to develop a sound science-based foundation on which to build a reliable and affordable safety classification of ENM and nanotechnologies. For example, we need a clear understanding of the relationship between ENM characteristics, such as their surface chemistry, and the biological changes they may evoke in living organisms throughout their life cycle. Reaching these goals would remove one major obstacle for realizing the full potential of these materials and technologies.

Essence of engineered nanomaterials enabling nanotechnologies
ENM constitute a large number of classes and subclasses of diverse materials that have features in common: one, two or three of their dimensions are 1–100 nm. If only one dimension equals or is less than 100 nm, they are nanoflakes, whereas two such dimensions suggest a fibrous or a tubular structure, and three dimensions equal to or less than 100 nm mean a ball-like structure. An example of the first case is graphene, of the second case single-walled (SWCNT) or multi-walled (MWCNT) carbon nanotubes, and ENM with three dimensions equal to or less than 100 nm include various metal oxide and metal nanoparticles (3).

ENM typically have a small size, large surface area, and large surface to volume ratio. Due to their large surface area, they are much more reactive than their larger but chemically identical counterparts. They exhibit unique properties not found in larger particles (4). For example, carbon nanotubes have tensile strengths better than that of stainless steel, and better electrical conductivity than copper. In addition, organic materials, such as nanocellulose fibres, exhibit unique properties including excellent electrical conductivity. It is, hence, not surprising, that these unique materials,
Knowledge gaps hampering the risk assessment of engineered nanomaterials

The fundamental equation in toxicology is hazard x exposure = risk. Thus if one can prevent hazards or exposure from occurring, there is no risk (10). The current challenge in assessing the potential health risks of ENM is the lack of knowledge on health effects and exposure to the very different classes and great diversity of ENM. There is no systematic database on hazards or exposure, or systematic identification of dose-effect relationships for any given ENM. The National Institute for Occupational Safety and Health (NIOSH) has drafted a proposal for occupational exposure levels (OEL) for nano-sized (0.1 mg/m$^3$) and micro-sized (2.4 mg/m$^3$) titanium dioxide based on their potential to increase the risk of lung tumours in experimental animals (11). Likewise, NIOSH has proposed a draft OEL of 7 μg/m$^3$ for CNT, based on their ability to produce inflammation and interstitial fibrosis as a result of pulmonary exposure (12). There have also been European attempts to define precautionary benchmark levels for different types of ENM, using technical methods to assess exposure to these materials (13). None of these proposed draft OELs or benchmark levels have been implemented, or have legislative power.

There have also been attempts to identify the routes of exposure in occupational environments, and the release of these materials into environmental compartments such as air, soil, and ground and surface waters, which leads to the exposure of consumers through air, water and food. The release of nanomaterials from products incorporating ENM has also been studied (14). These attempts have provided further insight and understanding of the potential human and environmental exposures, and of exposure routes throughout the entire life-cycle of ENM. However, none of these activities have provided the quantitative exposure information required for health or environmental risk assessment.

Analysis of risk assessment of engineered nanomaterials, and the way forward

Exposure to ENM

Exposure of workers and of the environment to ENM is possible at all stages of production, transport, storage, and the incorporation of ENM into products. This also includes the recycling of these materials. Workers have the greatest likelihood of exposure to ENM through the pulmonary route, because ENM occur as aerosols in the occupational environment. However, consumers may also be exposed via the skin when using, for example, sunblock creams or cosmetics (15).

In all the above stages; production, transport, storage, incorporation into the product, and recycling of ENM, these materials may also be leaked into different environmental compartments; air, soil, and surface and groundwater. This may allow transportation of ENM into drinking water, inhaled air, and food through contamination of crops and production animals, and lead to consumer exposure (16).

Workplaces at which exposure to ENM may take place require a thorough analysis of environments in which ENM are used. Schulte et al. (16) suggested that such workplaces should include the following: 1) research laboratories; 2) start up and scale up operations; 3) manufacturing of ENM on an industrial scale; 4) incorporation of ENM into products by their down-stream users (e.g. cosmetics industry); 5) disposal and end-of-life; and 6) recycling of ENM when they again become raw materials. The risk assessment challenges include reliable exposure assessment, including the ability to separate background nanomaterials from ENM. Without this information, the setting of occupational exposure limits for ENM is not possible (17).

Health hazards of ENM

Because it is not possible to discuss all the various ENM groups and their health effects, I will use carbon nanotubes (CNT) as an example in this context. The best-known classes of CNT are single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNT).

It has been demonstrated that in experimental animals, MWCNT may induce asbestos-resembling changes including mesothelial thickening and mesotheliomas in the peritoneal cavity of mice (7, 18). The results of these studies support each other (19) but are not suitable for risk assessment. Later studies have shown (20) that MWCNT, when exposed via the lungs, may reach the subpleural space and cause subpleural granulomas. Via the same route, they may also induce pulmonary fibrosis and inflammation (20, 21). NIOSH (12) has proposed a draft OEL of 7.0 μg/m$^3$ for CNT. Other proposals for different CNT...
that vary between 1–2 and 210 μg/m³ have also been proposed (22, 23). So far, none of these proposed OELs are implemented. A considerable challenge that remains is the development of intelligent testing strategies and safety assessment paradigms, which should allow the evaluation of the safety of increasing numbers and classes of ENM (15).

Management and governance of risks of engineered nanomaterials

Adequate risk assessment is an important prerequisite for risk management of ENM. Furthermore, trustworthy risk governance of ENM requires the dissemination of safety culture within the main communities dealing with ENM, notably the regulators, the industry, the labor unions, the research community, and the public at large. Trust is important for both the successful management and the governance of the risks of ENM.

Risk management approaches used in the EU are generally based on the REACH regulation (24). This novel regulation does not, however, provide reliable or sufficiently practical guidance on how to assess the potential risks of ENM, and hence, the support of REACH for ENM risk management and governance is limited. The most recent approaches include the promotion of safe-by-design thinking throughout the whole life-cycle of these materials, from planning, to design, and production. Including safety as an integral element in business thinking would mean enhanced understanding of the benefits of safety for realizing the promises of nanotechnologies. Supported by EU FP7 CP-IP 211464 (NANO-DEVICE).

References


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