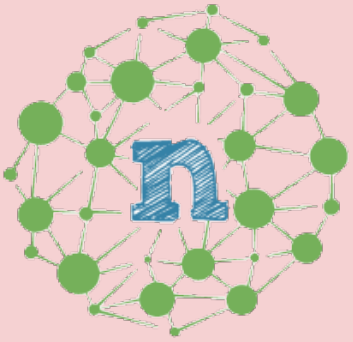
Risk Assessment of Nanomaterials in a Regulatory Context

- The concept of 'risk' refers to a combination of intrinsic hazard and exposure, which can be applied to nanomaterials in the same way as for traditional chemicals.
- Full assessment of risks for environmental and human health requires enough information on the hazards and the exposure scenarios for a substance, product, or technology in question.
- The use of traditional risk assessment tools for nanomaterials is currently limited by knowledge gaps about the nanomaterials on the market, their exact characterisation and intrinsic hazards.
- These limitations, along with the lack of legally binding guidance and risk assessment tools applicable to the specific properties of nanomaterials, represents a major obstacle to the safe use of manufactured nanomaterials.
- Governments and regulatory bodies should:
  - Ensure that manufacturers undertake appropriate testing of nanomaterials prior to their products being placed on the market.
  - Require producers to demonstrate the benefits of products and materials containing nanomaterials.
  - Make use of the precautionary principle to ensure avoidance of exposure to nanomaterials by all workers and human beings.



Introduction

The increasing amounts of products that contain nanomaterials give rise to concerns regarding their human health and environmental safety. Due to their small size, nanomaterials exhibit very specific properties that depend not only on their chemical composition, but also on their surface characteristics and shape (see Toxicity of Engineered Nanomaterials). Nanomaterials can therefore interact with organisms (plants, animals or humans) differently from other chemicals of the same chemical composition.[1] Some nanomaterials have been used in products on the market for decades. Examples of "traditional" nanomaterials are carbon black (used in tyres) or synthetic amorphous silica (used in toothpaste or as an anticoagulant in food products). Other nanomaterials like carbon nanotubes (CNT) (used as polymer additives, paints, coatings and fuel cells) and quantum dots (used in electronics and flat screen displays) were more recently introduced to the market.[2] To date, nanomaterials are used in a wide range of products, including mass applications such as toothpaste, sports equipment, and yoghurt to clothing, paint, batteries and cosmetics. The global market for nanomaterials has been estimated at 11 million tonnes per year.3

In theory, manufactured nanomaterials are subject to the same environmental, worker and health protection regulations as any substance or material. However, the effectiveness of the regulatory framework to address nano-specific risks is limited due to their specificities and continuing knowledge gaps about the environmental and health impacts of nanomaterials. Another hurdle for the effective enforcement of regulation is the lack of standardised testing methods for nanomaterials and ongoing disagreement on terminology and definitions.

The risk assessment (RA) process describes procedures to identify, evaluate, characterise, and interpret the risks of a substance. Governments and regulatory bodies use the outcomes of RAs to adopt risk-management measures, i.e.: the measures put in place to protect the health and safety of the public, consumers, workers and the environment from potential or identified risks.

This fact sheet provides an overview of the existing risk assessment procedures for manufactured nanomaterials as well as details and comments on the most relevant on-going developments.

Introduction

Possible impacts of manufactured nanomaterials (MNM) on human health or the environment are not yet fully understood. One of the challenges of risk assessment for nanomaterials is to define what nanomaterials actually are and how they differ from traditional chemicals or other pollutants.

This fact sheet focuses on MNM specifically produced to make use of their properties in a 'nano' form. This excludes naturally occurring nanomaterials, incidentally generated nanomaterials (those released or transformed from non-nano products), and process generated nanoparticles (such as from drilling, machining, abrasion, etc. of products, whether or not they contain nano). Existing risk assessment methods need to be adapted to the specificities of MNM and their specific properties because MNM properties differ from those of the same substances in non-nano-form (also called 'bulk' forms):

- Their small size enables them to pass through biological barriers in human beings and animals, making them transportable to cells and organs
- They can accumulate in human beings and animals following a different pattern from their 'bulk' counterparts
- Their high surface-area-to-volume ratio modifies interactions with biological systems such as humans, animals, and the environment

Scientific research in support of assessing MNM risks has been going on for at least a decade. Over time, a more systematic approach on RA has emerged in European Union funded projects and in OECD activities. Preliminary results are becoming increasingly available, but they remain relatively limited in scope. Further RA results are expected to be available in the future, and an elementary understanding of the (eco) toxicological effects of basic nanomaterials and the availability of risk assessment tools is expected for the year 2020.[4]

Risk Assessment

To better understand the role of risk assessment, it is necessary to understand what 'risk' means in the context of regulating substances or activities with potential harmful impacts on human health or the environment ('regulatory toxicology'). The overarching objective of safety regulation is to protect safeguarded subjects – usually human health and the environment – from harm. The regulation can be based on the inherent hazard of a given substance or activity, or on risk levels. In the case of risk-based regulation, Box 1 below provides definitions for the elements taken into consideration to identify relevant risk levels of chemical substances.

Box 1: Definition of risk used in regulatory toxicology

Risk = f(exposure) * f(hazard)

Exposure:
How much of a substance is a target organism exposed to over a certain time period (or taken up).

Hazard:
The intrinsic ability of a substance to disrupt biological processes in living organisms (toxicity).

REACH, the European horizontal regulation of chemical substances, includes risk assessment procedures[5] for the adoption of risk management measures. The main elements of the EU's risk assessment framework,[6] are briefly addressed below:

- risk hypothesis
- hazard identification
- hazard characterisation including dose-response assessment
- exposure assessment and evaluation
- risk characterisation
- risk assessment and evaluation

Risk hypothesis

A robust RA relies on a testable (falsifiable) risk hypothesis based on a precise identification of relevant sources of a given substance as well as suspected hazards to specific 'targets' such as human beings, animals or the environment. The hypothesis should answer key questions such as: "what/who is at risk?" and "what are they at risk of?"[7] An inadequate problem formulation can result in inappropriate risk analysis, and therefore in inappropriate risk management, misguided regulatory action or, more worryingly, inaction. Limited scientific understanding and data gaps in relation to possible sources, targets and impacts of nanomaterials are serious hurdles in adequate problem formulation.

Hazard identification

Hazard identification deals with 'known unknowns' within a range of known possibilities. Potential hazards are identified based on knowledge derived from experiences or preliminary scientific insights.

The OECD has stated that the majority of its existing test guidelines for 'bulk' chemical substances are generally applicable to MNM[8], particularly those in relation to end-points assessed[9], target organs[10], and effective dose[11]. However, there is no scientific consensus on the applicability of OECD test guidelines to nanomaterials, with only a small number of studies[12] supporting their adequacy for environmental fate and another study[13] concluding that environmental fate of nanomaterials cannot be reliably assessed with the existing guidelines.

Specific needs for new test guidelines have been identified: to specify dissolution behaviour and adsorption-desorption properties; to determine dispersion behaviour; and to identify transformation processes in environmental media.

Hazard assessment and evaluation

Hazard assessment identifies the capacity of a substance or material to cause harm to humans or environmental organisms when it is taken up at a certain dosage.[14] In traditional chemical toxicity testing, this is done by animal testing. Increasingly, chemical hazard assessment is done using in-vitro methods (the toxicological study of impacts on cells or tissues cultivated in a laboratory) reducing the reliance on animal testing. More recently, other alternative methods have been discussed to speed up hazard assessment, including grouping approaches and computer-aided modelling methods.[15]

For nanomaterials, important hazard assessment questions are: what are the physical-chemical properties of the nanomaterial? Where does the nanomaterial end up (at which end-point?); and what potential effect does the nanomaterial have on the given organism?

Exposure assessment and evaluation

Exposure assessment and evaluation aims to identify the extent to which people and/or the environment are exposed to a particular substance. Release of nanomaterials can occur at each stage of a product's lifecycle – manufacturing, transportation, use-phase, end-of-life treatment, and final disposal. In the context of risk assessment, points of potential exposure along the lifecycle need to be identified together with potential exposure levels for each of the points. For nanomaterials, little to no exposure information is available. Together with ongoing uncertainties about hazards and known hazards (e.g. such as for nano-silver, nano-zinc or CNTs), this situation gives rise to concerns over possible human health and environmental risks.

Risk characterisation

Risk characterisation is the estimation of the incidence and severity of adverse effects likely to occur in a human population (e.g. workers), other species, or an environmental compartment (air, water or soil) due to actual or predicted exposure to a substance. It also includes 'risk estimation', which is the quantification of that likelihood.[16] In the case of nanomaterials, risk characterisation requires adapted risk assessment tools that do not yet exist or have not yet proven to be appropriately adapted to nano. Therefore, adequate risk characterisation cannot yet be delivered.[17]

Risk assessment and evaluation

For robust decisions on risk management measures, scientifically sound results from previously mentioned elements are necessary. In the case of MNM, existing limitations or methodological gaps, (see next section) still prevent full risk assessments. Further research is needed to understand, for example, whether the (default) factors used in RA to extrapolate effects from one species (e.g. rats) to another (e.g. humans) are appropriate for the RA of MNM.[18]

Risk assessment as applied to nanomaterials

Using traditional risk assessment approaches, ensuring the safety of any given MNM on the market would require testing every single form of nanomaterial as well as all the products in which they are used for all possible exposure scenarios. Given the heterogeneity of MNM, this approach would require many decades to produce an adequate level of data. It would require vast amounts of resources to interpret the significance of the enormous amount of testing results. It would also require a large number of animal tests, which conflicts with animal welfare objectives.

To avoid these drawbacks, the case-by-case approach to regulating nanomaterials is giving way to 'grouping' alternatives, or approaches that could apply risk assessment results across different nanomaterials with comparable properties.

Risk assessment methodologies for nanomaterials are being discussed, evaluated and refined by several stakeholders aiming for a future with complete, scientifically valid, quantitative risk assessments of nanomaterials. Most notably, the OECD´s Working Party on Manufactured Nanomaterials (WPMN) created a working group on Risk Assessment and Regulatory Programmes which evaluates risk assessment approaches for manufactured nanomaterials through information exchange, and identifies opportunities to strengthen and enhance risk assessment capacity internationally (see Nanotechnology Regulation and the OECD).

Three frequently discussed alternative assessment methods are briefly assessed below. Although the terminology used by the different expert communities is not consistent, the methods could help to speed up the risk assessment of nanomaterials. The applicability of these methods continues to rely on an adequate set of data that is still rarely available for nanomaterials.

Grouping / categorisation

This approach suggests grouping or categorising nanomaterials on the basis of the assumption that specific physical-chemical, toxicological and ecotoxicological properties are likely to be similar hazard-indicators or to follow a regular pattern. This approach aims to eliminate the need to test each nanomaterial against each endpoint by deriving hazard statements from the generic data available for a group or category of substances.

Groups or categories of nanomaterials could be based on applying data:

- from a 'bulk' substance to one or several nano-forms of the same substance
- from one nano-form of a substance to several nano-forms of the same substance[19]
- between different substances (whether different nano-forms or 'bulk')

To date, only broad general nanomaterial groups based on physical-chemical properties have yet to be considered, including carbon-based, metals and metal oxides, tubes and wires. There is currently no unified global grouping concept with well-defined and generally accepted criteria for applying a nanomaterial grouping approach. Consequently, broad grouping concepts may introduce the possibility of overlooking certain hazards or underestimating adverse effects.

Irrespective of a unified concept, using a nanomaterial grouping approach faces significant challenges:

- The inherent complexity of nanomaterials means that their known characteristics such as the release of toxic ions, surface area, impurities, coatings, shape, and ability to cross biological barriers, may not be enough basis for robust grouping.
- Nanomaterials evolve as they age and may be transformed throughout their lifecycle, which may influence their toxicity. These phenomena and remaining knowledge gaps complicate the prediction of their toxicity[20] and consequently prevent a robust analysis of potential grouping or categorisation.

Work to address these issues is currently ongoing within the OECD WPMN, but results are not expected for a number of years[21] and no specific regulatory guidance on nanomaterial grouping is yet available in the European Union or elsewhere. The latest version of an OECD guidance document on grouping of chemicals explicitly excludes such guidance as premature.[22]

With current scientific knowledge, 'grouping' may notionally help speed up regulatory assessment processes while avoiding unwanted animal testing. However, key EU and international chemicals management bodies[23] acknowledged that these approaches can potentially introduce additional uncertainty into hazard and risk assessment, which could result in over- or under-regulation of a nanomaterial.[24]

These methods could still be useful for a preliminary assessment of the safety of nanomaterials. But they all need further development from theory to practice, scientific refinement, and standardisation.

Read-across

This approach aims to fill data gaps for a chemical by using surrogate data from another substance.[25] Information on an endpoint for a given chemical is predicted by using data for the same endpoint from another substance. Such an approach requires the chemicals to be similar on fundamental aspects, for example, on their structural configuration, or properties and/or activities at molecular level.

Read-across can be applied between two chemicals (analogue approach) or through a group or category of chemicals (category approach), and can be quantitative or qualitative. In the case of a quantitative read-across assessment, known value(s) of a property for one or a group of source chemicals is used to estimate the unknown value of the same property for a given chemical, e.g. obtaining a dose-response relationship. By contrast, qualitative read-across can only give "yes" or "no" answers.

Read across between nanomaterials is different from read-across between traditional 'bulk' substances because the source and target nanomaterials used in read-across are generally different forms of the same substance rather than different substances.[26]

QSAR

QSAR stands for Quantitative Structure-Activity Relationship and is based on the understanding that the chemical structure and therefore the physical-chemical properties of a molecule are directly responsible for biological activity, and that effects may be predicted from this relationship. QSAR is commonly used to predict the physical-chemical properties of 'bulk' chemical substances, so applying it to nanomaterials requires an adapted 'nano-QSAR'.

In theory, using a nano-QSAR would help to predict, for example, the cytotoxicity (toxicity to cells) of a metal oxide nanomaterial such as zinc oxide. However, the successful development of nano-QSAR models depends not only on the quality of experimental data, but also on the availability of sufficiently large data sets.[27] Data availability still poses restrictions for applying nano-QSAR as nanomaterial toxicity data continue to lack consistency, comparability and public accessibility.

The challenges for assessing the risks related to nanomaterials Nano-specific innovation and commercial applications of MNM continues to rise. The continuing state of emergence of nano-related technologies, materials and applications is characterised by incomplete scientific knowledge. This is combined with a lack of experience with these novel products and production processes. It is subsequently difficult to regulate the environmental, health and safety aspects of MNM. Knowledge gaps relating to the health and environmental impacts of MNM can lead to regulatory uncertainty and/or ineffective regulation (including over-regulation).

Key fundamental elements of scientific knowledge about nanomaterials remain elusive, despite years of efforts by international fora (see Box 2). The development of tools for a harmonised global approach to risk assessment of nanomaterials is equally difficult to achieve. The structural lack of quality data makes a robust risk assessment of nanomaterials almost impossible. This worrying situation is worsened by a hesitancy bordering on neglect by public authorities to adequately regulate nanomaterials within existing chemicals legislation, in the EU and other industrialised countries.

Substantial challenges continue to exist in terms of responsible governance of the safety of nanomaterials which can be grouped into four areas:

- ***Novelty***: The novelty of nanomaterials and their behaviour has required the creation of new fundamental scientific knowledge on basic elements of experiments and testing, from characterisation of the material tested, to the tests used to identify and characterise potential hazard.
- ***Complexity***: The inherent complexity of the materials – the importance of their size, shape, surface coating, etc. in influencing their functionality – and the high number of different forms of each nanomaterial contributes to uncertainty in safety and risk assessment. Testing each potential form of a nanomaterial would require decades of research before an adequate amount of robust data is available to appropriately assess their individual risks.
- ***Poor quality science***: Important weaknesses in scientific rigour applied to many experiments on nanomaterials has been exposed on a global scale, as the tested nanomaterials are not (well) described, questionable doses are tested, and inappropriate tests are undertaken to identify hazard potential. Many of these tests are useless as they are not repeatable, not comparable and of insufficient quality to be included in a highly-needed directory of studies.

Box 2: Building a harmonised global science base and risk assessment tools

Three international organisations cooperate in developing harmonised standards and testing guidelines to establish a global approach to the identification and characterisation of nanomaterials and their risk assessment. These organisations are the International Standardization Organization (ISO), the OECD (see the factsheet Nanotechnology Regulation and the OECD for more information), and the European Standardisation Organisation (CEN). ISO's Technical Committee was created in 2005, and both CEN's Technical Committee and the OECD's Working Party on Manufactured Nanomaterials were created in 2006. Despite more than ten years of intense scientific activities under these three organisations, important and fundamental data gaps still exist. A separate factsheet on standardisation (in both CEN and ISO) and nanomaterials will be published later in 2016.

- ***Absence of precaution***: Despite REACH text clearly stating that provisions of the regulation are underpinned by the precautionary principle, there is no evidence of this being applied to nanomaterials (as for other potentially and clearly problematic substances). This is the case even with increasing numbers of products containing nanomaterials being placed on the market. Fewer than ten nanomaterials have undergone limited risk assessment to date, specifically for the narrow application of UV filtering in sunscreens (through the EU's Cosmetics Regulation). In a far too simplistic approach, the European Commission creates a false conflict between precaution and EU competitiveness and innovation. As a result, the European Commission is delaying the adoption of legislation and refusing to implement existing legislation in relation to nanomaterials, to avoid potentially negative effects on growth and competitiveness.

In addition to these general challenges, an EU-funded project on regulatory toxicity testing (NANoREG[28]) identified the following ongoing serious knowledge gaps and scientific challenges to conduct proper risk assessment for nanomaterials[29]:

- Nanomaterial physico-chemical characteristics that

determine the release, exposure, behaviour and toxicological effects in the environment, species and humans are still not well understood.
- Nanomaterial fate and persistence in humans and the environment (impact of solubility, coatings, surface charge, etc. on bioavailability, translocation and toxic effects) are still not adequately understood.
- The transfer of nanomaterials between various environmental media (air, water, soil) remains unclear.
- Nanomaterial uptake-pathways in human beings and in target species (inhalation, ingestion, absorption) need to be better understood. The mechanisms and characteristics that determine how nanomaterials are distributed in organisms and the environment (tissue distribution and distribution in species, concentration in target organs) are especially unclear.
- It is not yet clear which characteristic (mass, particle number, surface area) gives the best correlation between exposure to nanomaterials and the observed toxicological effect.
- There are still no standardised methods for nanomaterial characterisation and toxicity testing.
- Implementation tools for regulators to use grouping in a risk assessment are missing.

So, a dual focus is needed to:
- Reduce and ideally eliminate on-going data gaps, and in the meantime
- Implement precaution-based legislation, ensuring that nanomaterial manufacturers undertake appropriate testing of MNM prior to their products being placed on the market, providing information from those test results to regulatory authorities.

Conclusions

Robust risk assessments of nanomaterials are still not possible after more than ten years of individual and international efforts on even the most fundamental aspects of nanomaterials. This includes how to characterise and measure them, which of their physical-chemical properties causes which effects in different biological systems, and how they behave within different biological systems.

Yet more and more products containing nanomaterials are being placed on the market, with little to no specific safety data available. In the context of uncertain risks, producers should be required to transparently demonstrate the benefits and safety of products containing nanomaterials.

The European Commission continues to drag its feet on adequate governance of nanomaterials, hiding behind incomplete data sets/knowledge gaps, with considerable and unjustified delays to revision of chemicals legislation and not respecting requirements in key pieces of legislation.

In such a situation governments and regulatory bodies should make use of the precautionary principle to ensure avoidance of exposure to nanomaterials for all humans (in particular workers) and the environment.

Endnotes

1. http://ec.europa.eu/health/scientific_committees/opinions_layman/en/nanotechnologies/l-2/6-health-effects-nanoparticles.htm (accessed 17.8.2016)
2. For an overview on nanomaterials and applications see Appendix 2 to EU Commission Staff working paper - types and uses of nanomaterials, including safety aspects SWD (2012) 288 final: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012SC0288&from=EN (as from 20.11.2016).
3. See Fn. 2
4. (RIVM) (2015), p. 26.
5. Owen and Handy (2007), p. 5582 (5585)
6. National Research Council (NRC).
7. OECD (2012), p. 8.
8. OECD (2012), p. 26.
9. OECD (2012), p. 25.
10. OECD (2012), p. 26.
11. OECD (2012), p. 8.
12. Hankin et al. (2011); Kühnel/Nickel (2014).
13. Schwirn et al. (2014).
14. For more details see factsheet "Toxicity of Engineered nanomaterials" Öko-Institut, ECOS & CIEL (2015), p. 2 ff.
15. Cf. for OECD level: Workshop on Categorization 17 - 19. September 2014 in Washington D.C. as well as an OECD background document "Grouping for Reach-across of Manufactured Nanomaterials: Some Concepts and Existing Approaches – Starting Points for Discussion (2016).
16. European Commission (2013), p. 7.
17. Bos et. al. (2015).
18. OECD (2012), p. 34.
19. ECHA/RIVM/JRC (2016).
20. OECD (2014), p. 103; Lynch et. al. (2014).
21. C.f. OECD (2014), p. 103. OECD (2016), in which the results of an OECD survey on approaches on nano grouping/ equivalence/ read across concepts for regulatory regimes are summarised.
22. OECD (2014), p. 104.
23. Arts et al. (2015).
24. Arts et al. (2015).
25. Cf. Read-across for conventional substances: ECHA (2015), Read-Across Assessment Framework.
26. ECHA/RIVM/JRC (2016), p. 6.
27. Richarz et. al. (2015).
28. See the homepage of NANoREG: http://www.nanoreg.eu/ (as from 20.11.2016).
29. RIVM (2015), p. 47. Cf. ECHA (2014).

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Many nanomaterials have been on the market for years and new nanomaterials as well as products enhanced by those materials continue to enter the market regularly. With increasing scientific and political interest, our understanding of these materials continues to grow while numerous questions about possible health and environmental impacts of nanomaterials remain.

It is crucial to ensure that nanomaterials bring about true societal and environmental benefits, with limited risks to human health and the environment.

In 2013, CIEL, and ECOS (the European Citizen's Organization for Standardization) and the Oeko-Institute launched a three-year project to support public interest and engagement for the safe and precaution based development of nanotechnologies and nanomaterials. This project is funded for three years by the Villum foundation.

The ultimate objective of the project is to ensure that risk assessment methodologies and risk management tools guide regulators towards the adoption of a precaution-based regulatory framework for the responsible development of nanomaterials in the EU and beyond.

The project partners participate in the work of the standardization organizations Comité Européen de Normalisation (CEN) and International Standards Organization (ISO). Project partners also participate actively in the work of the Organization for Economic Co-operation and Development (OECD) related to health, environmental and safety aspects of nanomaterials.

On the project web page you can find fact sheets introducing the basics relating to nanomaterials, position papers and policy recommendations, http://www.ciel.org/project-update/safe-development-of-nanotechnologies/.