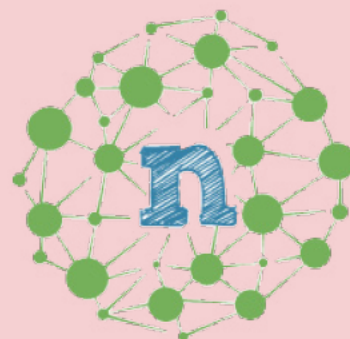# TOXICITY OF ENGINEERED NANOMATERIALS

- Nanomaterials show distinguished toxicological properties in comparison to the same substance in the non-nanoscale (bulk) form or in solution.
- A release of Engineered Nanomaterials (ENM) into the environment can occur at each stage of a product's life cycle, including manufacturing, transportation, use-phase, end-of-life treatment, and final disposal.
- The modes of ENM release and the transformations they undergo in the environment determine the exposure of environmental organisms and humans to ENM.
- The toxic impacts depend on the ENM type and on the intake dosage (how much for how long).
- The toxicity is a function of particle number and surface area rather than mass.
- The knowledge about the toxicity of ENM is still incomprehensive. Especially long-term environmental impacts and chronic health impacts remain unknown.
- Standards are indispensable for risk governance and must therefore be developed concurrent to the innovation process.

This factsheet intends to inform interested lay persons who engage in the field of risk governance for nanotechnologies, including standardization, labelling, or regulation in a European context. It reviews currently available knowledge on nano-toxicology[1], in particular exposure assessment and hazard assessment of engineered nanomaterials (ENM). The factsheet aggregates information gathered from scientific literature and attempts a preliminary interpretation of the status-quo in nano-toxicological risk evaluation.

The overarching term 'nano' refers to the size dimension, i.e. the diameter of single particles or their aggregates or the thickness of nano-layers. The term **'engineered nanomaterial' (ENM)** refers to anthropogenic materials at nano-scale that are "designed for a specific purpose or function" (ISO/TS 80004-1:2010). ENM can exist in environmental compartments if they have been released from the technosphere[2]. ENM are usually designed to fulfil desired technical functions, and they are manufactured by means of technical processes. The scope of this factsheet encompasses ENM, consisting of deliberately synthesised nano-objects (products) as well as unintended (by-)products (formed by accident, as emissions or contaminations from synthesis reactions, or waste). Nanomaterials show distinguished physicochemical properties in comparison to non-nanoscale materials. For more details about the questions around the definition of nanomaterials, please refer to the factsheet on definitions of Nanomaterials (ECOS & CIEL, 2014).

The regulatory toxicology must be based on tangible facts. Under REACH[3], the toxicological risk characterization covers the analysis of exposure scenarios and the quantitative hazard assessment (toxicology). The **magnitude of exposure** can be estimated by measurements or by probabilistic modelling (Gottschalk et al 2013). Moreover, for the hazard assessment, scientific evidence about the dose–response relationship must be established as a measure of the **toxic hazard potential.** The latter can be achieved by experimental animal testing (in vivo) or by the use of non-animal (in vitro) methods, such as read-across, grouping of substances and quantitative structure activity relationships (QSARs). However, a

1. If it is not further differentiated, in this text the term "toxicology" covers the study of human toxicity aspects as well as aspects of environmental toxicity.
2. Nanomaterials originating from nature are outside the scope of this factsheet although they may possess the same degree of toxicity as engineered nanomaterials.
3. REACH is the European regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals

Figure 1: The Nano-object

ENM consist of nano-sized objects (e.g. particles) showing a variety of shapes and internal structures. The shape factor is a crucial aspect in the toxicological assessment of ENM. ISO/TS 80004-6:2013 specifies the term nano-objects as follows:
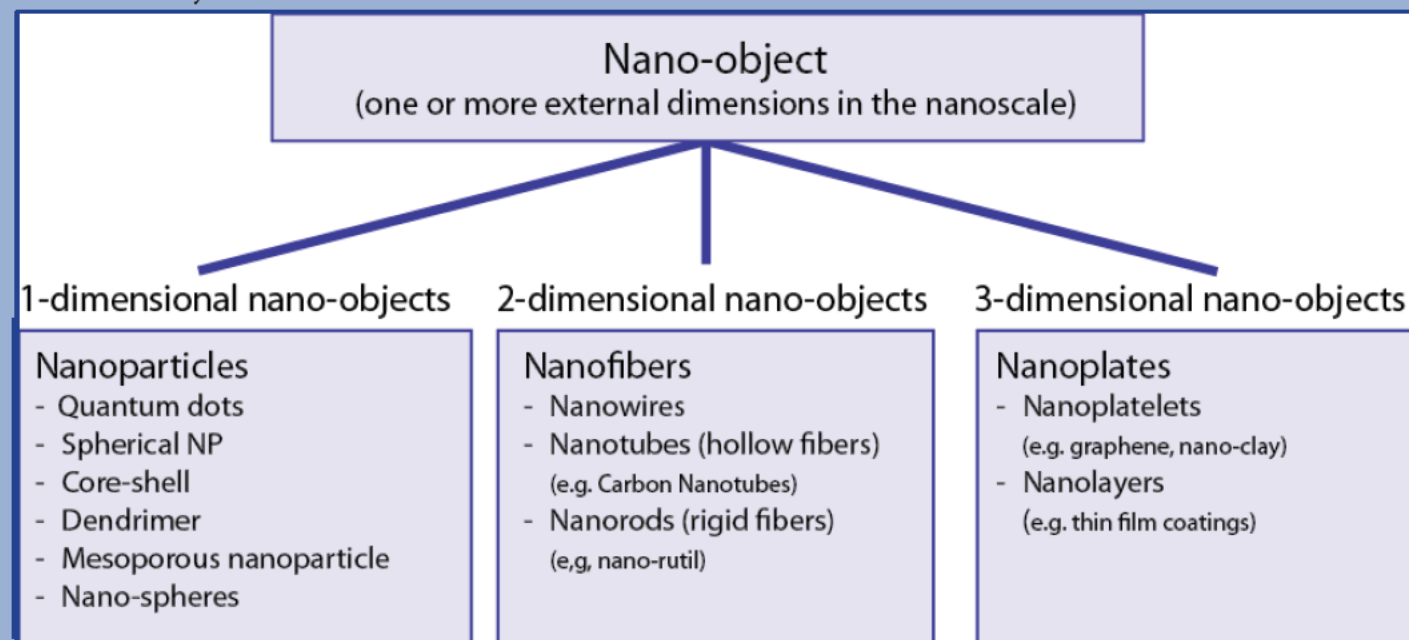
Nano-object
(one or more external dimensions in the nanoscale)

1-dimensional nano-objects

Nanoparticles
- Quantum dots
- Spherical NP
- Core-shell
- Dendrimer
- Mesoporous nanoparticle
- Nano-spheres

2-dimensional nano-objects

Nanofibers
- Nanowires
- Nanotubes (hollow fibers)
  (e.g. Carbon Nanotubes)
- Nanorods (rigid fibers)
  (e,g, nano-rutil)

3-dimensional nano-objects

Nanoplates
- Nanoplatelets
  (e.g. graphene, nano-clay)
- Nanolayers
  (e.g. thin film coatings)

Figure 1: Categories of ENM according to ISO TS 27687

risk cannot always been described in a quantitative manner. For specific endpoints and specific substance properties (such as bioaccumulation and persistency), a thorough understanding of cause-effect chains is necessary. The toxico¬logical evaluation of dose-response relationships and their underlying mechanisms is a multistep scientific process. In other words, a lot of research has to be done before the safety of environment and health from potential risks posed by ENM can be ensured.

Supplementary to scientific knowledge, the assessment of toxicological risks necessitates standardized definitions and methods. Standards are indispensable for toxicology studies to arrive at meaningful results that are open to comparison and interpretation. This includes specifications for the planning, implementation, sample preparation, as well as data processing of measurements. Moreover, the development of standards for detection, identification, and measurement of nano-objects is a precondition for monitoring and controlling

risk mitigation measures, including the protection of occupational and consumer health as well as environmental health.

Exposure assessment: the release of ENM and how they get into contact with organisms

Exposure assessment describes how much of a substance comes into contact with a target organism (e.g. humans). Exposure can occur once a pollutant has been dispersed in the working or natural environment following a release from technical systems. The level of exposure depends on a variety of aspects, such as substance concentration, likelihood and duration of contact, bio-availability etc. Even a toxic substance does not cause harm without a target organism being exposed to it. For instance, complete technical enclosure of a hazardous substance[4] can avoid environmental and human exposure in the first place (Fig. 2: the lion in a cage). Exposure control by safe containment is a preferred risk mitigation strategy in industry. However, any technical system provides

safety only up to a certain degree, depending on its economic feasibility. This means: even in normal operation some emissions take place continuously. In order to reduce them further, more costly exposure control methods (e.g. filters) or even remediation (cleaning up the source of pollution) are necessary. Realistic exposure scenarios have to describe the conditions of use and the risk management measures in a quantitative manner. Possible failure modes need to be adequately taken into consideration. A product life-cycle perspective helps to understand the sometimes complex pathways of ENM release, transports, exposure, and uptake by organisms (Hischier & Walser 2012). Figure 3 gives an overview of possible sources of ENM released from nano-products and their fate until exposure.
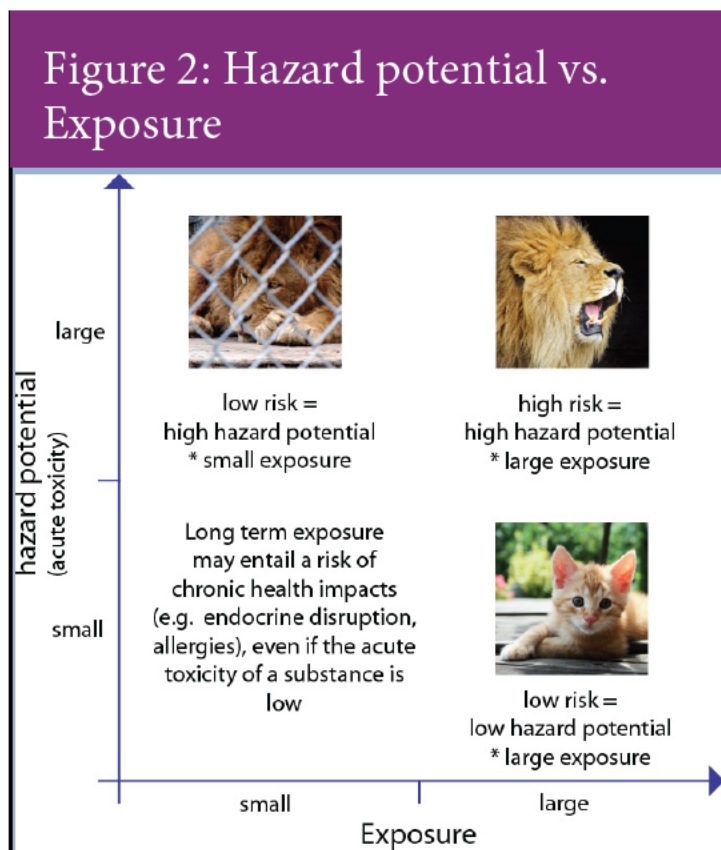
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4. REACH says: "use under strictly controlled conditions"

5. A risk is understood as the possibility of environmental or health damage. 'Possibility' refers to the uncertainty of occurrence (how big is the exposure?) as well as the uncertainty about the hazard (how toxic are ENM?).

6. The same substance may have diverse toxic impacts on different organisms.

Box 2: The toxicological risk assessment approach

In the field of regulatory toxicology, a risk[5] i s expressed as the function of exposure and hazard (the severity of impacts). In other words, the possible damage to health or ecosystems depends on dosage and toxicity (OHSAS, 18001:2007). This notion of risk encompasses two independent aspects (Fig. 2):

1. Exposure: the likelihood and the extent to which organisms (including humans) come into contact with ENM. Exposure describes the amount of ENM to which an organism is subjected over a certain time period.

2. Toxicity: the intrinsic ability of a substance to disrupt biological processes in living organisms (hazard potential). This factor describes the inherent property of a certain ENM, and depends on physical/chemical substance properties as well as the nature of the target organism[6].

The unintentional release of ENM from products is often not anticipated or taken into account prior to their commercialization. ENM could be released during primary production processes (synthesis), formulation and application of intermediate products, waste treatment as well as accidents that may occur at each stage of a product life cycle. Human exposure may also re-sult from direct contact, for instance due to ingestion of nano-food additives, medical nano-applications, or use of cosmetics. Exposure may lead to uncontrolled and incidental intake of ENM and impair human health (Saunders 2009). The actual exposure to ENM also depends on the transformations that they under-go up to the time at which they come into contact with organisms (Jośko & Oleszczuk 2012). For instance, carbon-nanotubes may be released and become air-borne during recycling and disposal of nano-textiles or batteries, and can thus cause unexpected exposure at the working place and in surrounding areas (Köhler et al. 2008; Roes et al. 2012).

Complex systemic effects do often arise when advanced technologies are applied in societal and economic realities. Synergistic effects can amplify the risks (for

Figure 2: Hazard potential vs. Exposure

low risk = high hazard potential * small exposure

high risk = high hazard potential * large exposure

Long term exposure may entail a risk of chronic health impacts (e.g. endocrine disruption, allergies), even if the acute toxicity of a substance is low

low risk = low hazard potential * large exposure

hazard potential (acute toxicity)

large

small

Exposure

small

large

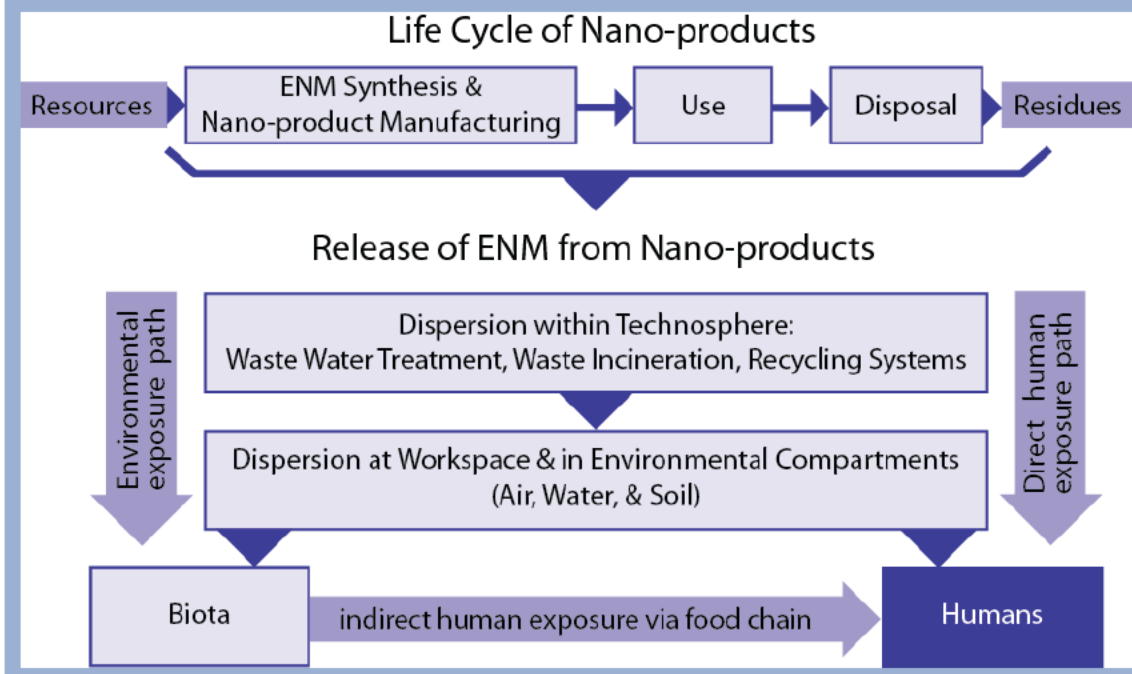## Figure 3: Life Cycle of Nano-products

Figure 3: Exposure pathways from ENM release to human and environmental impacts (Köhler & Som 2014)

instance if other hazardous chemicals are involved) (Wang et al. 2011). Furthermore, the mitigation of exposure risks at one stage in the product life cycle may lead to risk migration (e.g. tight sealing of ENM in products may hinder them to escape during the use phase, but they may be liberated due to recycling processes). Such complex interactions are hard to anticipate ex-ante as exemplified by Mitrano et al. (2014) who investigated the release and environmental exposure pathways of silver nano-particles used in textiles.

Box 4: ENM release

Release of ENM can occur at each stage of the life cycle, notably:

- emissions and release during production and manufacturing processes,
- handling and disposal of production waste,
- leaks during transportation,
- accidents during production and transportation,
- detachment from products during their use phase (intended or unintended),
- emissions during recycling processes and final disposal of nano-enabled products.

Hazard assessment: the toxicity of engineered nanomaterials

The hazard assessment describes the inherent toxic properties of a substance or material, that is, the capacity to inflict damage on living organisms[7] when it is taken up at a certain dosage. The magnitude and duration of exposure determines the dosage that a target organism can absorb. A higher dose with short duration of exposure may cause acute toxic effects whereas long-term exposure at low doses may lead to chronic health effects or cumulative environmental impacts.

The toxicity of most substances follows a non-linear dose-response relationship: at small doses, no adverse impacts can be observed (effects can even be whole-some as in the case of pharmaceuticals) until the ex-posure exceeds a certain substance-specific threshold above which adverse impacts occur. Among scientists, there is a growing awareness for certain toxicological mechanisms (such as endocrine disruptors) for which a minimum effect threshold [8]cannot be identified with certainty. A hazard potential should not be neglected even at low dosage because adverse long-term impacts cannot be ruled out until counterevidence has been es-tablished.

7. The term "organism" refers to humans as well as organisms in the environment.

Mechanisms of Nano-toxicity

There appears to be no scientifically justified size threshold at which an abrupt change from macroscopic to nano-scale modes of toxicity could be observed. ENM are likely to be more biologically active than the same quantity of non-nanoscale (bulk) materials having the same chemical composition. Most toxicologists agree that biological effects (including toxicity) emanate from the surface of particles. The surface area of ENM is much larger than bulk material (see Figure 4). The fact that ENM interact with organisms mainly via their surface makes it difficult to define adequate measurands of dosage. A dose-response relationship, established for a certain quantity of larger-sized particulate materials, will therefore gradually change if particles are smaller. A mass-based dosage metric is therefore inadequate for nanomaterials. Hence, the standardization of measurands for dosage of ENM should make reference to indicators representing the biologically active surface area (e.g. particle number and size distribution), rather than mass.
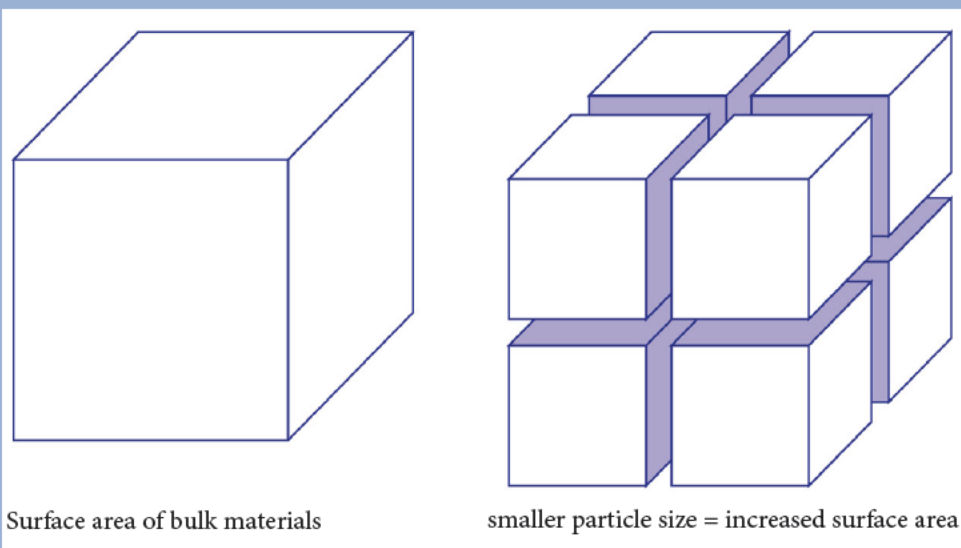
Whether or not there is a specific mode of nano-toxicity other than increased surface activity is currently subject of scholarly debate. Some authors point at nano-specific toxicokinetic mechanisms such as uptake via respiratory and dietary mechanisms or transcytosis, bio-kinetics (distribution of ENM within the body), endocytosis (translocation of ENM on a cellular level) (Krug & Wick 2011; Kunzmann et al. 2011; Oberdörster et al. 2005). Donaldson und Poland (2013) disagree with the concept of nano-specific toxicity, arguing that "there is no evidence that particles below 100 nm, the threshold definition of a NP, show any step-change in their hazard, meaning that there is no evidence of novel 'nano-specific hazard'".

The absence of a distinct size threshold, however, does not mean that nano-specific toxicity effects can be ruled out. The toxic mechanisms at nanoscale are subject to on-going research. Josko et al (2013) summarize two toxicological interpretations, which are currently discussed in literature:

1) The "free ion activity model" (FIAM) and the "biotic ligand model" (BLM). According to these models, toxic activity emanates from metal ions that are liberated from metallic or oxidic nano-objects that have penetrated living cells. ENM act as a carrier for the cytotoxic potential at cellular level.

2) The other model attributes the toxicity of nanomaterials to the production of free oxygen radicals. Reactive oxygen species (ROS) damage cell membranes, enzymes, DNA and any other cell organelles.

The following summarizes the most relevant nano-toxicological effects on humans and natural

Figure 4: Illustration of the relationship between particle size and surface area

Surface area of bulk materials

smaller particle size = increased surface area

8. No Observed Effect Level or Concentration (NOEL/NOEC)

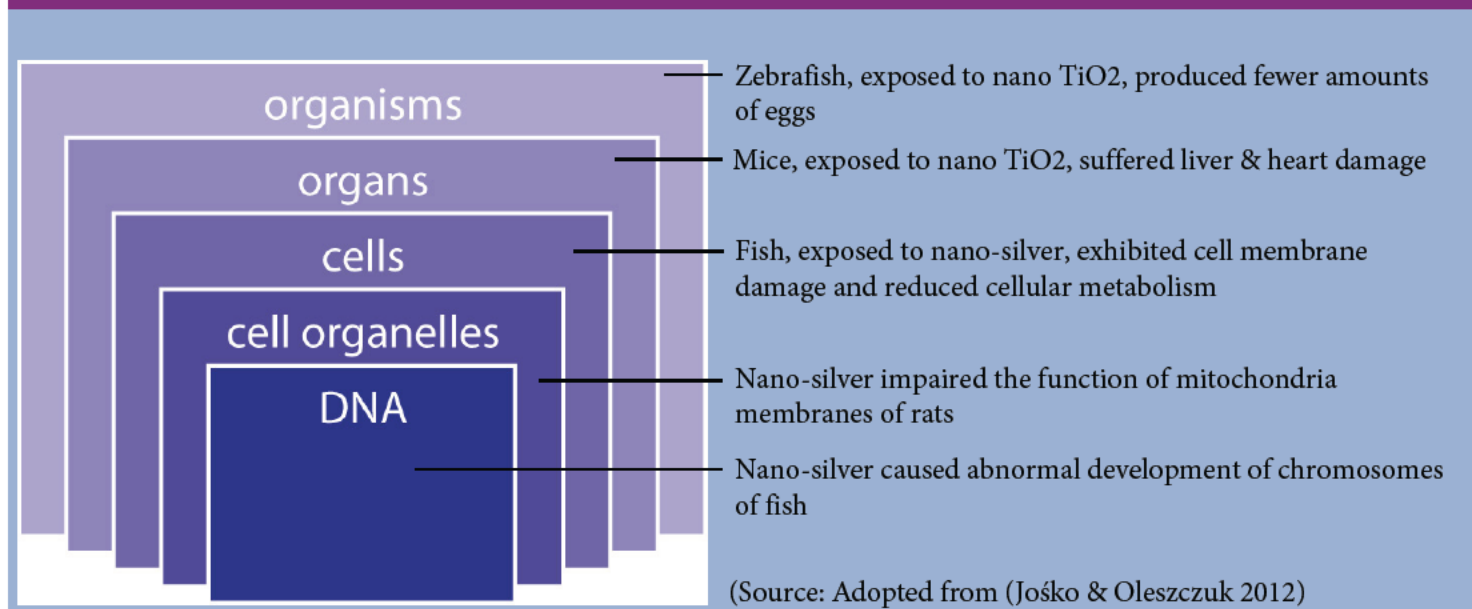organisms as discussed in contemporary research literature:

- Oxidative stress: ENM can induce the formation of Reactive Oxygen Species (highly reactive molecules with free outer electrons) within organisms. The free radicals oxidise the surrounding organic matter and thus cause damage. Nanoparticles can trigger additional formation of free radicals and increase inflammatory reactions (Simkó 2011).

- Inflammation: ENM can, due to their high surface reactivity and large numbers, lead to a chronic overload of immune system cells that are responsible for removing foreign substances from the body.

- Genotoxic potential: possibility of DNA damage due to cellular uptake of ENM or chronic inflammatory response of immune cells. The DNA damage may result in cancer (Doak et al. 2012). Mutagenic effects were observed on bacteria (Kumar et al. 2011).

- Reproductive nano-toxicity: various types of ENM can act as endocrine disruptors. Iavicoli et al (2013) conclude from a broad review of research literature that ENM may disturb the reproductive systems of male (e.g. gonadal cell viability) as well as female organisms (e.g. effects on ovarian structural cells). Larson et al. (2014) observed that cellular exposure to gold nanoparticles disturbs the estrogen production in female organisms. Nano zinc-oxide and nano-silver inhibited the male sperm production as well as sperm mobility in in-vivo studies on mice and rats. However, the scientific evidence of these experimental observations is still insufficient.

- Mechanical interaction and tissue changes: Incorporated ENM can accumulate in body tissue (e.g. lung) and become immobilized by immune reactions. Accumulation of large amounts of foreign particles can clog normal tissue functions and lead to chronic diseases (Mossman et al. 2007-05-30).

- Other possible effects: protein and lipid damage, enzyme disruption.

The toxicokinetic[9] mechanisms of nanomaterials seem to differ from the non-nanoscale form of the same substance. It has been observed that certain ENM can be easier absorbed by living organisms than dissolved chemicals or larger particles. Some ENM can infiltrate into organisms because natural elimination mechanisms or the immune system work ineffective at the size range of nanomaterials. Inhaled carbon nanotubes, for instance, seem to overstrain the alveolar

Figure 5: Impact of nanomaterials on living organism

organisms — Zebrafish, exposed to nano TiO2, produced fewer amounts of eggs

organs — Mice, exposed to nano TiO2, suffered liver & heart damage

cells — Fish, exposed to nano-silver, exhibited cell membrane damage and reduced cellular metabolism

cell organelles — Nano-silver impaired the function of mitochondria membranes of rats

DNA — Nano-silver caused abnormal development of chromosomes of fish

(Source: Adopted from (Jośko & Oleszczuk 2012)

9. Mechanisms by which substances are absorbed in a living organism, organ or cell (i.e. absorption, metabolism, distribution, and elimination/excretion)

macrophages when they are trying to clean them from the lung. This can lead to inflammation. Some ENM can, due to their smallness, translocate inside the body to places which are normally protected by natural barriers. In-vivo studies on mice showed that titanium dioxide nanoparticles (n-TiO2) can cross the placenta barrier and cause complications during pregnancy (Yamashita et al. 2011). Concern has been voiced that similar effects could happen to humans who are increasingly exposed to n-TiO2 in form of sunscreen and cosmetic products (Buerki-Thurnherr et al. 2012). Observations on aquatic organisms suggest that ENM are able to percolate through cell membranes and interfere with vital processes (e.g. mitochondrial metabolism). Certain metallic nanoparticles were also found to cause DNA damage without even crossing cell barriers (Bhabra et al. 2009). In contrast, non-nanoscale variants of the same substance would not be able to enter living cells. This indicates that observed nano-toxicity effects are the result of complex biological interactions.

While the aforementioned toxic effects result from unintended uptake of EMN, there are also opportunities to use such mechanisms for the good. Pharmaceutical research investigates the possibility of using nanomaterials as vehicles for controlled drug delivery. ENM are hopeful candidates for novel pharmaceutical agents, e.g. for cancer therapy. As always when novel pharmaceuticals are developed, it is paramount to thoroughly assess possible adverse side effects. This must encompass the toxicity of these agents after being metabolized and excreted into the environment.

ENM released from products may exhibit a different toxicity than pristine ENM, which are used for toxicity tests (Nowack et al. 2012). In the environment, physical and chemical (abiotic) transformations and biotic metabolism can change the properties of ENM and thus influence their toxicity. Examples of abiotic influences on ENM are: technical treatment (incineration, heating), dissolution, transportation, agglomeration/aggregation (nanoparticles tend to clump together), absorption (ENM stick to other surfaces), sorption (chemicals stick to ENM surfaces), sedimentation etc. (Lowry et al. 2012; Wang et al. 2013). Moreover, chemical changes to free ENM and their functionalized surface can occur (e.g. by oxidation). Such modifications in natural media influence the bioavailability of ENM (the amount of uptake in organisms at certain exposure levels). Biotic processes along natural food chains, such as bio-accumulation and bio-magnification, can increase the exposure and enhance the bioavailability (Judy et al. 2011; Werlin et al. 2010). Humans, being often at the top position of natural food chains may thus become exposed to higher concentrations of ENM in seafood (Klaine et al. 2008).
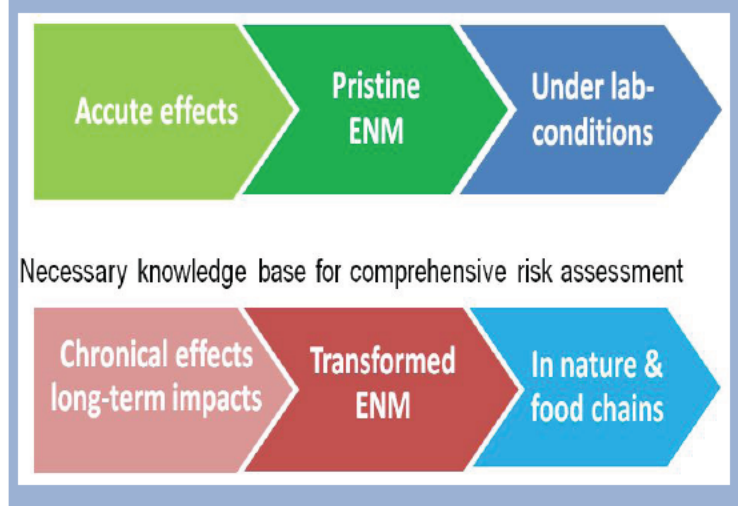
Eco-toxicity risks

Eco-toxicological research investigates the question how organisms in terrestrial and aquatic eco-systems are affected by exposure to free ENM. Thus far, the scientific knowledge about the impacts of ENM on natural organisms remains incomplete. In spite of a growing body of research literature, it is too early for conclusive answers about the severity of the risk related to the eco-toxicity of ENM. Predictive eco-toxicological models covering various types of ENM and indicator organisms are not yet available.

A number of recently published review papers in the field of eco-toxicology conclude that ENM carry the risk of eco-toxic impacts. Observation made by in-vitro as well as in-vivo studies support the hypothesis that the bioavailability of ENP is very specific to the type of nanomaterials as well as to transformations they undergo in the environment (Chen et al. 2011). Moreover, environmental conditions, including exposure to other pollutants, determine how tolerant organisms are against ENM. Josko et al (2013), reviewing a broad body of research literature, found numerous observations of toxic impacts on natural organisms, as diverse as protozoa, bacteria, fungi, crustaceans, amphibians, plants, and mammals including humans. The modes and degree of toxic impacts is varied and strongly depends on the concrete ENM exposure and target organism under study. In addition, the specific environmental conditions (e.g. freshwater/seawater, pH-level etc.) play an important role as well as the functionalisation of ENM. Matranga & Corsi (2012) conclude that bioaccumulation and bio-magnification of ENM can occur along trophic chains. This may increase the risk of human exposure through the consumption of contaminated food such as fishery products.

Knowledge and uncertainties

For the majority of ENM that are already used in industry and in products, the current magnitude to exposure to ENM in daily life remains uncertain. The toxic hazards and the magnitude of exposure are hard to assess due to a lack of transparency regarding amount and type of industrially produced ENM and their incorporation in products. Moreover, the fate of ENM in the environment and their complex interactions are not fully understood. Regarding toxicity, the current knowledge base contains white spots about uptake & interaction with biological matter. For instance, the observation that ENM may act as endocrine disruptors raises concern regarding the long-term

Figure 6: Knowledge base for risk assessment

Necessary knowledge base for comprehensive risk assessment

impact of low dosage exposure. Such may occur under normal circumstances of nano-materials production and applications. In spite of numerous toxicological in-vitro and in-vivo studies published up to now, it remains challenging to compare them and draw conclusions regarding risk levels. The investigation of chronic effects on human health and the environment requires toxicological long-term monitoring.

Science cannot easily mitigate the uncertainty since risk research is lagging behind the rapid progress in innovation of nanotechnologies. One of the reasons for scientific uncertainty has been a lack of standardized definitions, measurement methods, and lab-procedures. A comparative review of toxicological studies by Krug & Wick (2011) showed a clear lack of standardization in study design and reporting of

toxicity indicators. The management of nano-specific risks therefore remains challenging, and falls into the domain of policy as pointed out by the European Environmental Agency (Hansen et al. 2013). The report identifies nanotechnologies as an application area for the precautionary principle. It advises not to use incomplete knowledge as a reason to postpone risk-preventive actions (Som et al. 2010). To this end, the early stage of nanotechnological innovation offers good opportunities to address the toxicity of ENM before any adverse impacts occur at large scale following the proliferation of nano-enabled products on the global mass market. The effective governance of environmental health and safety aspects of ENM depends on access to credible data about what ENM are currently being produced (or developed), in what quantity, and in which products they are integrated. This data must be made public to facilitate independent risk assessment.

Glossary

In-vitro studies: test the toxicity of a substance under laboratory conditions outside of living organisms (in-vitro = in a test glass). Living cell-lines or DNA molecules in artificial culture medium are exposed to a controlled dosage, and the toxic effects on the level of cells are studied isolated from the complex biological processes of whole organisms. In-vitro studies are used as a quick toxicity test for new substances, but the findings cannot easily be linked to health impacts on the whole organism.

In-vivo studies: test the impacts of ENM on living organisms under laboratory conditions (in-vivo = in the living). Test animals are exposed to a controlled dosage of ENM and the toxic responses are monitored. In classical toxicology, in-vivo tests are used to determine the lethal dose of pollutants. The so-called LD50 test establishes which dose is lethal to 50% of test animals (e.g. rats) exposed to a certain chemical. In-vivo studies with animals are often used as a model for human toxicology, but the transposition of their results to humans is often not directly possible.

Epidemiological studies: analyze the patterns of health impacts in a defined human popu¬lation being exposed to a certain contaminant. Thus far, there is a paucity of epidemiological studies on the health impacts of ENM (because they are new), but there is an abundance of studies on health impacts of air pollution with fine and ultrafine particles (< PM 2.5). There is epidemiological evidence for adverse health impacts of exposure to ultrafine particles (e.g. welding fume). In regard to ENM, however, the evidence of adverse effects is inadequate due to a lack of verified exposure data.

Relevant Standards and Specifications

Published by International Organization for Standardization, ISO ISO/TC 229 [10]:

ISO 10801:2010	Nanotechnologies - Generation of metal nanoparticles for inhalation toxicity testing using the evaporation/condensation method
ISO 10808:2010	Nanotechnologies - Characterization of nanoparticles in inhalation exposure chambers for inhalation toxicity testing
ISO/TS 12025:2012	Nanomaterials - Quantification of nano-object release from powders by generation of aerosols
ISO/TR 12802:2010	Nanotechnologies - Model taxonomic framework for use in developing vocabularies -- Core concepts
ISO/TR 12885:2008[11]	Nanotechnologies - Health and safety practices in occupational settings relevant to nano-technologies
ISO/TS 12901-1:2012	Nanotechnologies - Occupational risk management applied to engineered nanomaterials -- Part 1: Principles and approaches
ISO/TS 12901-2:2014	Nanotechnologies - Occupational risk management applied to engineered nanomaterials -- Part 2: Use of the control banding approach
ISO/TR 13014:2012	Nanotechnologies - Guidance on physico-chemical characterization of engineered na-noscale materials for toxicologic assessment
ISO/TR 13121:2011	Nanotechnologies - Nanomaterial risk evaluation
ISO/TR 13329:2012	Nanomaterials -- Preparation of material safety data sheet (MSDS)
ISO/TR 16197:2014	Nanotechnologies - Compilation and description of toxicological screening methods for manufactured nanomaterials
ISO/TS 27687:2008	Nanotechnologies -- Terminology and definitions for nano-objects -- Nanoparticle, nanofibre and nanoplate
ISO 29701:2010	Nanotechnologies -- Endotoxin test on nanomaterial samples for in vitro systems -- Lim-ulus amebocyte lysate (LAL) test

In preparation by ISO ISO/TC 229:

ISO/NP TR 16196	Nanotechnologies -- Compilation and description of sample preparation and dosing methods for engineered and manufactured nanomaterials
ISO/AWI TR 18401	Plain language guide -- Explanation of core terms with examples
ISO/AWI TR 18637	General framework for the development of occupational exposure limits for nano-objects and their aggregates and agglomerates
ISO/AWI TS 18827	Nanotechnologies -- Electron spin resonance (ESR) as a method for measuring reactive oxygen species (ROS) generated by metal oxide nanomaterials
ISO/AWI TS 19006	DCFH-DA assay for evaluating nanoparticle-induced intracellular reactive oxygen spe-cies (ROS) production
ISO/AWI 19007	Modified MTS assay for measuring the effect of nanoparticles on cell viability
ISO/NP TR 19057	Nanotechnologies -- Use and application of cellular in vitro tests and methodologies to assess nanomaterial biodurability
ISO/NP TS 19337	Nanotechnologies -- Use and application of cellular in vitro tests and methodologies to assess nanomaterial biodurability
ISO/NP TR 19601	Nanotechnologies -- Nano-object aerosol generators for inhalation toxicity studies

10. http://www.iso.org/iso/home/store/catalogue_tc/catalogue_tc_browse.htm?commid=381983

11. Under revision as of end 2014

References:

Bhabra, G.; Sood, A.; Fisher, B. et al (2009). Nanoparticles can cause DNA damage across a cellular barrier. Nature Nanotechnology, 4(12), 876–883.

Buerki-Thurnherr, T.; von, M. & Wick, P. (2012). Knocking at the door of the unborn child: engineered nanoparticles at the human placental barrier. Swiss Medical Weekly.

Chen, Z.; Yadghar, A.M.; Zhao, L. & Mi, Z. (2011). A review of environmental effects and management of nanomaterials. Toxicological & Environmental Chemistry, 93(6), 1227–1250.

Doak, S. H.; Liu, Y. & Chen, C. (2012). Chapter 14 - Genotoxicity and Cancer. In: Fadeel, B.; Pietroiusti, A.; Shvedova, A. (Eds.), Adverse Effects of Engineered Nanomaterials 243–261. Boston: Academic Press.

Donaldson, K. & Poland, C.A. (2013). Nanotoxicity: challenging the myth of nano-specific toxicity. Nanobiotechnology • Systems biology, 24(4), 724–734.

Gottschalk, F.; Sun, TY.; Nowack, B. (2013). Environmental concentrations of engineered nanomaterials: Review of modelling and analytical studies. Environmental Pollution 181: 38. 287-300

Hansen, F.S.; Maynard, A.; Baun, A.; Tickner, J.A.; Bowman, D.M. (2013). Nanotechnology - early lessons from early warnings. In: European Environment Agency (2013). Late lessons from early warnings: science, precaution, innovation. Report: No 1/2013.

Hischier, R. & Walser, T. (2012). Life cycle assessment of engineered nanomaterials: State of the art and strategies to overcome existing gaps. Science of the Total Environment, 425(0), 271–282.

ISO/TS 80004-1:2010 Nanotechnologies – Vocabulary – Part 1: core terms

Iavicoli, I.; Fontana, L.; Veruscka Leso, V. & Bergamaschi, A. (2013). The Effects of Nanomaterials as Endocrine Disruptors. Int. J. Mol. Sci., 14, 16732-1680.

Jośko, I. & Oleszczuk, P. (2012). Manufactured Nanomaterials: The Connection Between Environmental Fate and Toxicity. Critical Reviews in Environmental Science and Technology, 43(23), 2581–2616.

Judy, J. D.; Unrine, J. M. & Bertsch, P. M. (2011). Evidence for Biomagnification of Gold Nanoparticles within a Terrestrial Food Chain. Environmental Science & Technology, 45(2), 776–781.

Klaine, S.J.; Alvarez, P.J.; Batley, G.E. et al (2008). Nanomaterials in the environment: behavior, fate, bioavailability, and effects. Environmental Toxicology and Chemistry, 27(9), 1825.
Köhler, A.R. & Som, C. (2014). Risk preventative innovation strategies for emerging technologies the cases of nano-textiles and smart textiles. Technovation, 34(8), 420–430.

Köhler, A. R.; Som, C.; Helland, A. & Gottschalk, F. (2008). Studying the potential release of carbon nanotubes throughout the application life cycle. Journal of Cleaner Production, 16(8–9), 927–937.

Krug, H.F. & Wick, P. (2011). Nanotoxikologie - eine interdisziplinäre Herausforderung. Angewandte Chemie, 123(6), 1294–1314.

Kumar, A.; Pandey, A. K.; Singh, S. S.; Shanker, R. & Dhawan, A. (2011). Cellular uptake and mutagenic potential of metal oxide nanoparticles in bacterial cells. Chemosphere, 83(8), 1124–1132.

Kunzmann, A.; Andersson, B.; Thurnherr, T.; Krug, H.; Scheynius, A. & Fadeel, B. (2011). Toxicology of engineered nanomaterials: Focus on biocompatibility, biodistribution and biodegradation.

Biochimica et Biophysica Acta. 1810(3), 361–373.

Larson, J. K.; Carvan, M. J. & Hutz, R. J. (2014). Engineered Nanomaterials: An Emerging Class of Novel Endocrine Disruptors. Biology of Reproduction, 91(1), 20.

Lowry, G.V.; Gregory, K.B.; Apte, S.C. & Lead, J.R. (2012). Transformations of Nano-materials in the Environment. Environmental Science & Technology, 46(13), 6893–6899.

Matranga, V. & Corsi, I. (2012). Toxic effects of engineered nanoparticles in the marine environment: Model organisms and molecular approaches. Marine Environmental Research. 76(0), 32–40.

Mitrano, D.M.; Rimmele, E.; Wichser, A.; Erni, R.; Height, M. & Nowack, B. (2014). Presence of Nanoparticles in Wash Water from Conventional Silver and Nano-silver Textiles. ACS Nano. 8 (7), 7208–7219.

Mossman, B. T.; Borm, P. J. & Vincent, C. (2007). Mechanisms of action of inhaled fibers, particles and nanoparticles in lung and cardiovascular diseases. Part Fibre Toxicol.4(4).

Nowack, B.; Ranville, J.F.; Diamond, S. et al (2012). Potential scenarios for nanomaterial release and subsequent alteration in the environment. Environmental Toxicology and Chemistry, 31(1), 50–59.

Oberdörster, G.; Oberdörster, E. & Oberdörster, J. (2005). Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles. Environmental Health Perspectives, 113(7), 823–839.

Roes, L.; Patel, M. K.; Worrell, E. & Ludwig, C. (2012). Preliminary evaluation of risks related to waste incineration of polymer nanocomposites. Science of the Total Environment, 417–418(0), 76–86.

Saunders, M. (2009). Transplacental transport of nanomaterials. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 1(6), 671–684.

Simkó, M. (2011). Nanoparticles, free radicals and oxidative stress. ITA Nanotrust Dossiers.

Som, C.; Berges, M.; Chaudhry, Q.; Dusinska, M.; Fernandes, T. F.; Olsen, S. I. & Nowack, B. (2010). The importance of life cycle concepts for the development of safe nanoproducts. Toxicology, 269(2–3), 160–169.

Wang, D.; Hu, J.; Irons, D. R. & Wang, J. (2011). Synergistic toxic effect of nano-TiO2 and As(V) on Ceriodaphnia dubia. Science of the Total Environment, 409(7), pp. 1351–1356.

Wang, F.; Yao, J.; Chen, H.; Yi, Z. & Xing, B. (2013). Sorption of humic acid to functionalized multi-walled carbon nanotubes. Environmental Pollution, 180(0), 1–6.

Werlin, R.; Priester, J.H.; Mielke, R.E.; et al. (2010). Biomagnification of cadmium selenide quantum dots in a simple experimental microbial food chain. Nature Nanotechnology, 6(1), 65–71.

Yamashita, K.; Yoshioka, Y.; Higashisaka, K. et al (2011). Silica and titanium dioxide nano-particles cause pregnancy complications in mice. Nature Nanotechnology, 6(5), 321–328.