



Review

MANAGEMENT OF HEALTH RISK RELATED TO USE OF ENGINEERED NANOMATERIALS. AN ANALOGY WITH BIOSAFETY

Dimiter Prodanov

Environment, Health and Safety, Imec, Belgium

ABSTRACT

*Safety of nanomaterials is a new scientific field, which draws increasing attention in literature. Among the challenges the field is facing are the insufficient amount and quality of nanotoxicological data and the ambiguity in the metrics describing the exposure. This results in substantial difficulties in the actual quantification of risk in terms of dose-response relationships and exposure limits, which are a cornerstones of chemical risk assessment. While there is no golden standard for risk assessment and management several pragmatic systems have come into being. All of these employ some form of categorization and grouping of (nano)materials into hazard groups. The present review aims to draw analogies between the nascent field of nanosafety and the well established field of biosafety, where the risk is also difficult to quantify. **Biomed Rev 2017; 28:104-109.***

NANOMATERIALS

The nanomaterials are broadly defined as those materials that have a certain percentage of particles at the nanoscale between 1 and 100 nm (see below). Particles of this size can get deposited in the lungs, pass easily through alveoli or even disperse in the body. While the size cut-off is somehow arbitrary it nevertheless conveys the important fact that properties of the features at nanoscale (i.e. nanoforms) can substantially differ from the properties of “macro” materials in bulk. Such desirable characteristics can include increased strength of the material, its chemical reactivity or altered electrical properties. These features offer possibilities for new applications in a broad range of sectors; for example in medicine (e.g. detection of genetic sequences using DNA-tagged gold nanoparticles); environment (e.g. waste-water treatment with carbon nanotube filters); or energy production (e.g. solar cells using silicon nanocrystals). At the same time, the use of manufactured nanomaterials in a number of commercial applications raises questions regarding potential unintended risks for the

workers, consumers and the environment.

Top-down and bottom-up approaches to nanotechnology

Nano-enabled technologies have been with mankind for centuries, if not millennia. What, however, makes modern nanotechnology unique is the aspect of deliberate exploitation of the nanoscale: Nanotechnology by definition uses intentionally desirable properties of materials at the nanoscale to deliver economically beneficial effects. From technological perspective there are two complementary approaches: top-down and bottom-up processing. While the bottom-up approach can be broadly identified as particle synthesis, or self-assembly; top-down approach can be thought of growth or deposition on surfaces. An example of the latter is micro or nano-electronics industry. Nanomaterial manufacturers typically employ bottom-up approaches, while end-user industries incorporate engineered nanomaterials on macroscopic objects, e.g. products like computer chips, tires, sportswear. From industrial end-user perspective the innovation cycle leads to new materials

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Correspondence and reprint request to Dimiter Prodanov, Kapeldreef 75, 3001, Leuven, Belgium. Tel: +32 16 28 18 40; E-mail: dimiter.prodanov@imec.be; dimiterpp@gmail.com

and nanoforms being introduced in manufacturing. Typically, the product development runs ahead of establishing metrics for the occupational and environmental hazards of these materials. Examples include nanoelectronics, automotive, cosmetics and painting industries.

INTERNATIONAL EFFORTS AND EU INITIATIVES IN NANOSAFETY RESEARCH

Traditional chemical risk assessment tools are based on a quantitative dose-response relationship, which is augmented by setting a threshold defining the no-effect levels, or occupational exposure limit (OEL). This type of risk assessment is applicable in cases when sufficient toxicological and occupational exposure data are available. Understanding properties of engineered nano-materials and how they affect living systems, such as the human body, draws substantial attention in recent scientific literature (Fig. 1). While the predominant number of studies are focused on the materials, relatively smaller amounts discuss more comprehensive safety questions.

It becomes increasingly clear that harmful properties of nanoforms sometimes do not correlate with the toxicological profile of the bulk materials. There are several reasons for that, notably the change of scale leads to a relative increase of the fraction of particles which are on the surface of the nano-object. The curvature and charge density also increase with the decrease of size. One of the challenges in nano-toxicology is therefore, the identification of the best metric for toxicological assessment (11). While traditional metrics are based on mass concentration, the majority of authors at present favor particle number based metrics.

A related challenge is how a nanomaterial can be defined as there are several different definitions internationally. According to the current recommendation by the European Commission a nanomaterial means:

A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimen-

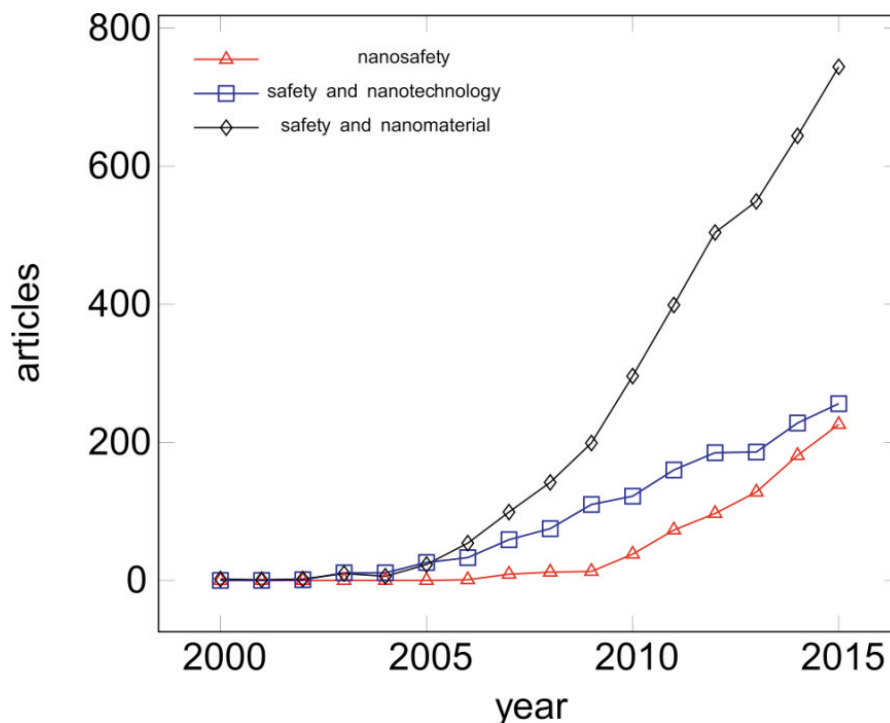


Figure 1. Number of article per year according related to safety of nanotechnologies according to key word combinations. Records were collected come from the PubMed database using the trend tool from (5).

sions is in the size range 1 nm - 100 nm.

In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %. By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.

On the other hand, ISO defines a nano-object simply as “material with one, two or three external dimensions in the nanoscale”, that is between 1 and 100 nm. To address so-outlined scientific and regulatory challenges international bodies, such as the European Union and the Organisation for Economic Co-operation and Development (OECD), have orchestrated substantial efforts. For example, the EU NanoSafety Cluster (www.nanosafetycluster.eu) is a network of projects in the funding programs FP6 (2002–2006), FP7 (2007–2013), and H2020 (2014–2020) framework programmes, intended at harmonizing the European Commission-funded in nanosafety research. Over that time, more than 50 projects have been associated with the NanoSafety Cluster.

Challenges in the risk assessment approach can be traced to the assumption that the hazard and the risk can be quan-

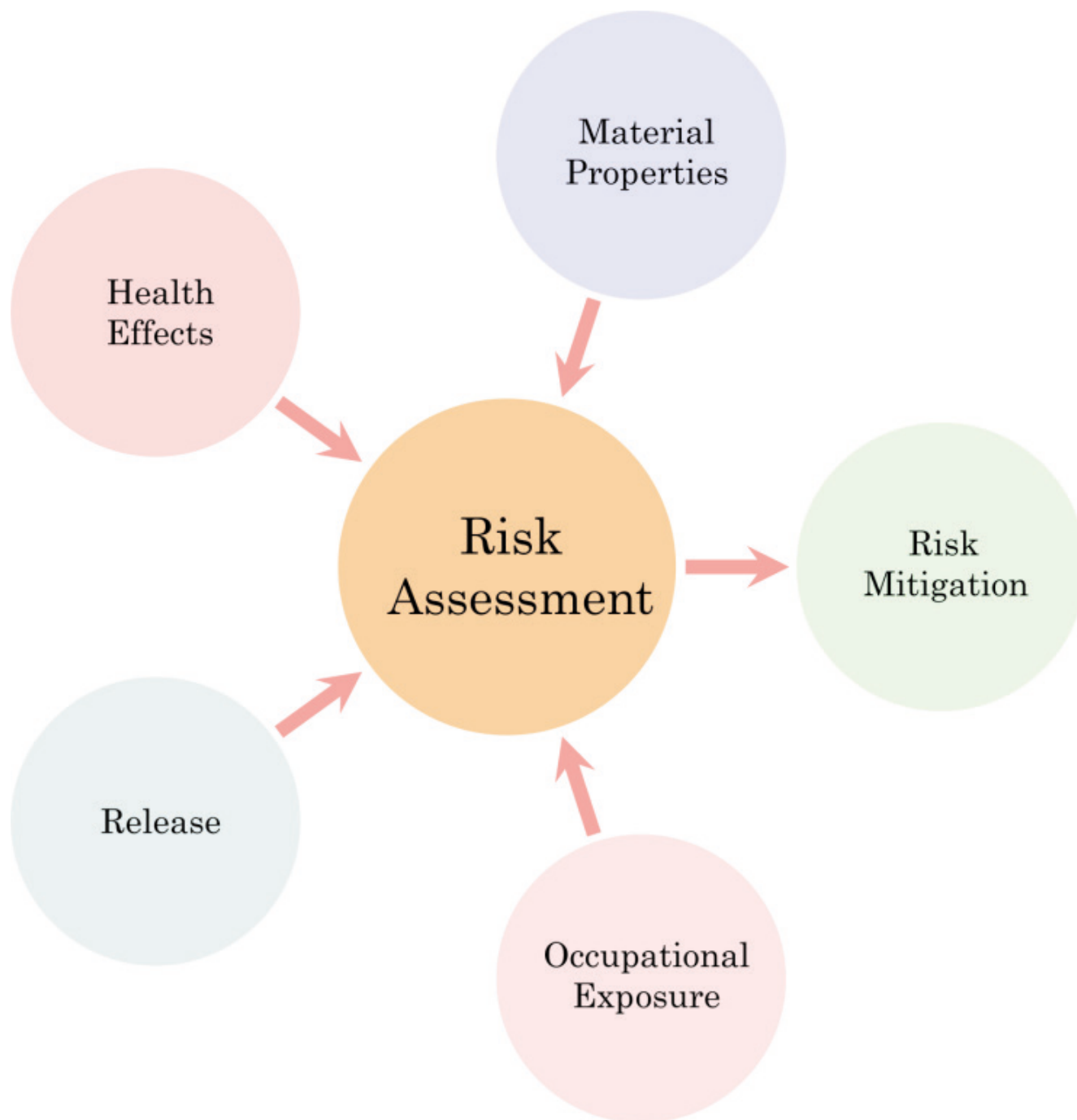


Figure 2. Holistic view of risk management as implementation of the Safe-by-design principle.

tified. From the biosafety practice, we know that this may not (ever) be the case. A holistic view of the nano-hazard and the related process risk is crucial for successful integration of nanosafety aspects into the overall risk management methodology. Material properties, health effects, potential of release and occupational exposure are principal aspects for successful risk mitigation (Fig. 2).

It is currently believed that conventional risk assessment tools have limited applicability to nanomaterials (3, 4, 6, 8, 11). This is due to several factors, mainly insufficient hazard characterization data and the lack of standards of reference methods and nanomaterials. A summary can be given as follows:

1. Insufficient hazard characterization leads to limited availability of data on physico-chemical properties, (eco)tox-

Table 1. Risk and control banding tools

Tool	Type	Result	Interpretation	Reference
ISO standard	Decision tree	Categorical	Preventive control	ISO 2014
Imec	Survey	Categorical	Occupational risk assessment	Van Hoornick <i>et al</i> , 2016
CB Nanotool	Score	Semi-quantitative	Preventive control	Paik, Park, 2009
ANSES	Decision tree	Categorical	Preventive control	ANSES, 2010
Nano Stoffenmanager	Decision tree + Score	Categorical	Risk prioritization	Duuren-Stuurman <i>et al</i> , 2012

icological properties and the environmental fate information, all of which are pre-requisites for comprehensive risk assessment. This insufficiency stemmed from the fact that nanomaterials of the same type can exhibit different properties due to the difference in synthesis method, therefore, the results obtained from one study might not generalize, thus rendering their use limited (3, 4, 6).

2. Poorly designed experimental protocols can lead to false positive or negative toxicological results because nanoparticles have been shown to directly interfere with the biological/toxicological assays used. Recent publications have demanded for a uniform standard operating procedures so that results obtained from different studies can be comparable and that a more concrete conclusion can be drawn (6, 8).

3. Additionally, due to the lack of data, occupational exposure limits (OELs) for most types of nanoparticles are unknown (NIOSH 2009; 11). The OELs for bulk parent materials can significantly differ from their nano counterparts due to the unique physico-chemical properties exhibited in the nano form and therefore, the two OELs are not interchangeable.

4. The best metric (by mass, concentration or number) for nanoparticles exposure characterization is still debatable.

While there is no golden standard for risk assessment and management several pragmatic systems have come into being. So identified gaps in understanding promote the view that the most promising approaches for management of nano-related risk are the risk and control- banding tools (Table 1), which are akin to the biohazard grouping. Efforts in the direction of grouping of nanomaterials and read-across missing properties of nanoforms are encouraged by the stakeholders, such as the nanotechnology industry, national regulators and international bodies, like OECD. There is a recent international standard dealing with nanosafety in occupational settings: ISO Technical Standard ISO/TS 12901-2:2014 “Nanotechnologies - Occupational risk management applied to engineered nanomaterials”. The standard is focused on intentionally produced nano-objects, such as nanoparticles, nanopowders, nanotubes, nanowires, as well as of aggregates and agglomerates and is focused on the management of the inhalation hazard. The standard defines 5 nanohazard groups which combine with four exposure bands (Table 2). This is constrained by 5 control bands, which identify measures to be implemented in order to reduce the risk for the personnel.

Table 2. Hazard grouping according to ISO/TS 12901

ISO Hazard class	Definition	Examples
Category A	No significant risk to health	Non-toxic soluble nanoparticles
Category B	Slight Hazard – Slightly toxic	-
Category C	Moderate Hazard	-
Category D	Serious hazard	-
Category E	Severe hazard	Carcinogenic insoluble nanoparticles, insoluble fibers, such as carbon nanotubes

Table 3. Biohazard classification according to EU Directive 2000/54 and WHO. Examples are given according to the Belgian state regulations. AAV - Adeno-associated virus, HBV – Hepatitis B Virus, HCV – Hepatitis C Virus, HIV – Human Immunodeficiency Virus

Biohazard class	Definition	Examples
Group 1	Biological agent that is unlikely to cause human disease.	<i>E. coli</i> K 12 strain AAV
Group 2	Biological agent that can cause human disease and might be a hazard to workers; it is unlikely to spread to the community; there is usually effective prophylaxis or treatment available.	Most strains of Influenza A virus
Group 3	Biological agent that can cause severe human disease and present a serious hazard to workers; it may present a risk of spreading to the community, but there is usually effective prophylaxis or treatment available.	HBV, HCV, HIV
Group 4	Biological agent that causes severe human disease and is a serious hazard to workers; it may present a high risk of spreading to the community; there is usually no effective prophylaxis or treatment available.	Ebola virus, Marburg fever virus

WHAT CAN WE LEARN FROM BIOSAFETY?

In biosafety practice, there are 4 biohazard groups and 4 major biocontainment levels (Table 2). Biosafety levels are based on a composition of facility design features, containment infrastructure, specialized equipment, work practices and operational procedures required for working with agents from the four risk groups (13). The emphasis is on the classification of biological agents based on the similarity of their action on a healthy human being. That is, the risk is measured in a relative way! This pragmatic classification provides the backbone for management of biorisk in laboratory setting for more than 20 years.

The current expert opinion identifies grouping criteria as priority in nanosafety research (11). In contrast to biosafety practice, in nanotechnology, each step of a process where nanomaterials are used or produced is assigned a particular risk level, which in turn determines the appropriate risk control measures. In my view, there are a number of synergies between both fields that can be exploited for cross-fertilization of the efforts. This is an open field of research, which may lead us out of the maze of conflicting nanotoxicology reports.

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