



Global challenges in the risk assessment of nanomaterials: Relevance to South Africa

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Internationally, there are efforts to develop standardised toxicity testing and risk assessment methods for engineered nanomaterials (ENMs). To this end, health risk assessments need to be conducted on ENMs synthesised in South Africa. Country-specific risk characterisation requires specific exposure assessments for those ENMs for which the likelihood exists for occupational and environmental exposure in that country. A challenge in hazard identification and risk assessment related to ENMs, regardless of country of origin, is that data on toxicity, carcinogenicity, pharmacokinetics, and occupational or environmental exposure are generally not available for most ENMs. Although the mechanisms previously identified as important in the toxicity and carcinogenicity of particles and fibres may be applicable, the possibility exists that the unusual physicochemical properties of ENMs may give rise to unique, and as yet unidentified, adverse effects. Moreover, generalised exposure scenarios that consider the life cycle of the agent have not been developed and are needed for the complete risk characterisation of ENMs. As health risk assessment is both resource and labour intensive, it is imperative to identify the aims of such an exercise prior to embarking on large-scale projects, to ensure that the data most useful for public health decision-making is provided. Identifying priorities in South Africa, in coordination with international efforts, can facilitate the effective use of research efforts for risk assessment and risk management decision-making.

Background

Health risk assessments are required for new technologies and for new classes of materials introduced to the market for human use. Amongst the most extensive regulation in this area is the European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) programme.¹ Risk assessment strategies based on categories of nanomaterials have been proposed, with consideration given to their physicochemical properties and modes of action.^{2,3} These categories are: carbon-based (fullerenes and carbon nanotubes), metal-based (quantum dots, nanogold, nanosilver and metal oxides), dendrimers and composites.^{4,5}

It is anticipated that workers and researchers handling these diverse engineered nanomaterials (ENMs), as well as the general public that use these products, will to some degree be exposed to, and therefore potentially at risk from, their adverse effects.⁶ Agencies and organisations in several countries have issued guidelines on good work and consumer practices for the handling and use of ENMs,^{7,8} and have formulated approaches for the evaluation of ENMs under existing health and safety regulations.⁵

A global effort to develop standardised testing procedures for risk assessment is led by the Organization for Economic Cooperation and Development (OECD). A list of priority ENMs has been developed and country sponsors have been identified⁹ (Table 1). South Africa is the sponsor for the most recent addition to this list, gold nanoparticles (AuNP); the USA is a co-sponsor, and the European Commission (EC) and Korea are contributors. The OECD standardised testing procedures include information on physicochemical characterisation, biotic systems, degradation and accumulation, and health effects.¹⁰ Phase I testing (introduced in 2007) includes the selection of the ENMs and the end points to be studied (Table 2). Phase II involves the evaluation of critical issues identified in Phase I or the performance of additional tests, including long-term tests and risk assessment. Data sharing of the tested ENMs will increase the efficiency of generating data needed for hazard and risk assessment.¹⁰

The Department of Science and Technology (DST) in South Africa has also emphasised the need for risk assessment of ENMs presently synthesised in the country.¹¹ Without reliable data on effects and exposure, in-depth risk assessments of ENMs in South Africa and other countries may be limited. It is therefore essential to coordinate international efforts and develop standardised methods for *in-vitro* and *in-vivo* hazard identification to provide data for the risk assessment of representative



ENMs within major categories. The purposes of this review are to, (1) provide an overview of risk assessment history and practice, (2) describe coordinated international research efforts in which South Africa participates and (3) discuss challenges in health risk assessment and areas of prioritisation for South Africa.

Overview of health risk assessment of nanomaterials

The objective of human health risk assessment is to provide scientific information based on toxicology or epidemiology data (if available) to predict or estimate risk associated with exposure to potentially hazardous substances. Traditionally, health risk assessment involves four steps (proposed in 1983 by the US National Research Council)¹²: (1) hazard identification, (2) dose–response assessment, (3) exposure assessment and (4) risk characterisation (Figure 1). Throughout each step of this process, uncertainties involved in making estimates also need to be considered.^{4,13}

Examples of the use of risk assessment for risk management decision-making include regulatory measures for establishing standards for water and air quality or requirements for environmental clean-up. Through the identification of potential sources and pathways of exposure for a population, and the determination of the health hazards associated with

exposure, risk characterisation describes the potential risk of a substance, from those that present little or no concern, to those that are likely to cause adverse effects. Risk assessment supports evidence-based risk management decisions and facilitates societal evaluation of acceptable risk.¹⁴

Basically, it is anticipated that the risk assessment of ENMs will follow the traditional risk assessment paradigm used for conventional chemicals.^{4,12} Nanoparticle-specific data are also needed in applying the risk assessment process and to determine if there are any novel properties of nanomaterials that may result in unique toxicity. New strategies and methods may be needed to identify and consider any factors that may be specific to certain ENMs.^{15,16}

Hazard identification

The first step in risk assessment is to evaluate the available hazard data, including that of *in-vitro* or *in-vivo* toxicity. The purpose of hazard identification is to identify the contaminants that may pose health hazards and to identify the conditions under which they could be toxic to humans.¹²

The potential hazards of a great number of ENMs have as yet not been identified. Numerous past investigations of inhaled particles and fibres have identified properties that determine toxicity as well as the mechanisms involved in this toxicity.

TABLE 1: List of nanomaterials and their country sponsors for toxicity testing.

Nanomaterial	Lead sponsor(s)	Co-sponsor(s)	Contributors
Fullerenes (C ₆₀)	Japan, USA	-	Denmark, China
Single-walled carbon nanotubes	Japan, USA	-	Canada, France, Germany, EC, China, BIAC
Multiwalled carbon nanotubes	Japan, USA	Korea, BIAC	Canada, France, Germany, EC, China, BIAC
Silver nanoparticles	Korea, USA	Australia, Canada, Germany, Nordic Council of Ministers	France, the Netherlands, EC, China, BIAC
Iron nanoparticles	China	BIAC	Canada, USA, Nordic Council of Ministers
Titanium dioxide	France, Germany	Austria, Canada, Korea, Spain, USA, EC, BIAC	Denmark, Japan, UK, China
Aluminium oxide	-	-	Germany, Japan, USA
Cerium oxide	USA, UK/BIAC	Australia, Spain	Denmark, Germany, Japan, Switzerland, EC, the Netherlands
Zinc oxide	UK/BIAC	Australia, USA, BIAC	Canada, Denmark, Germany, Japan, the Netherlands, Spain, EC
Silicon dioxide	France, EC	Belgium, Korea, BIAC	Denmark, Japan
Dendrimers	-	Spain, USA	Austria, Korea
Nanoclays	BIAC	-	Denmark, USA, EC
Gold nanoparticles	South Africa	Korea, USA	EC, Korea

Source: Organization for Economic Cooperation and Development, OECD.^{9,10} EC, European Commission; BIAC, Business and Industry Advisory Committee.

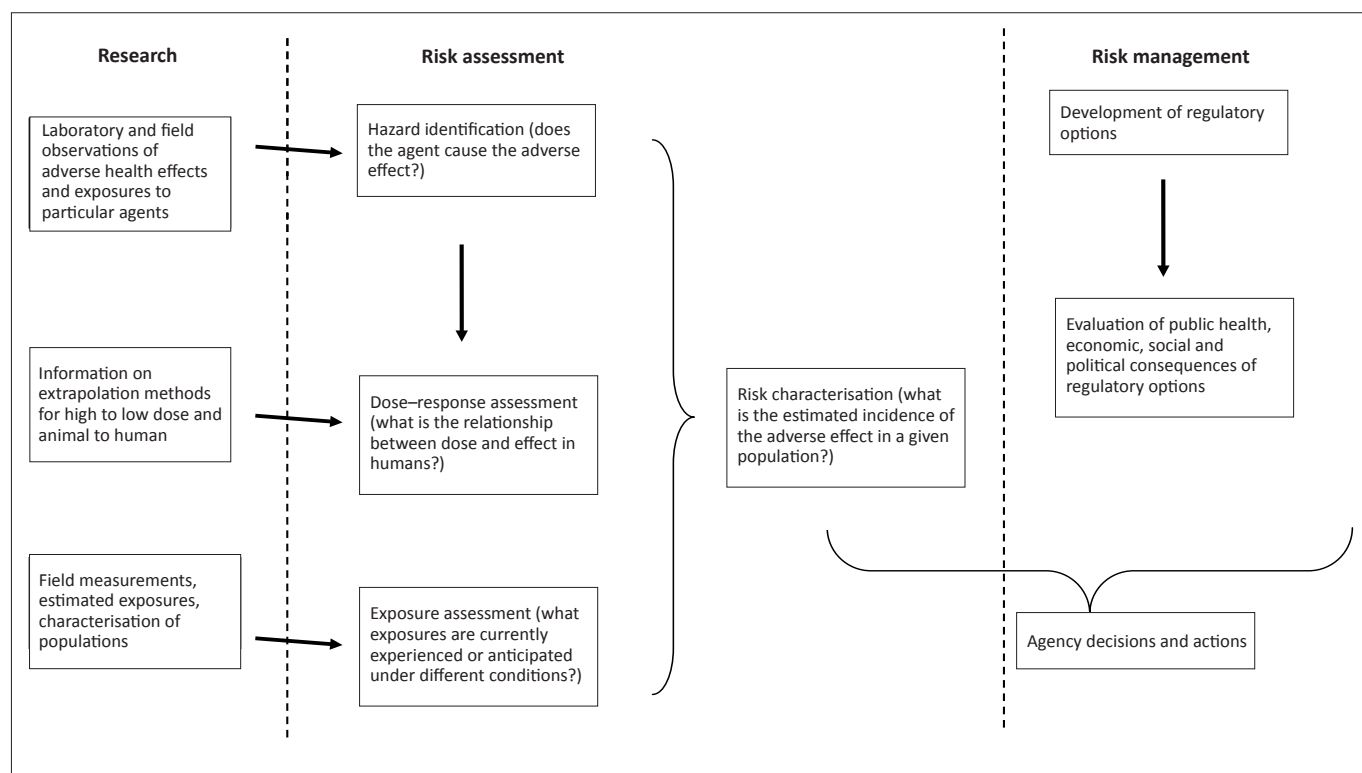
TABLE 2: List of end points to be studied in Phase I of the country-sponsored testing programme.

Testing category	Physical and biological measures (examples)*
Nanomaterial identification and information	Chemical name, identity (CAS number, EC number if available), structural formula or molecular structure, composition (purity, additives, coatings, etc.), spectral data, commercial uses, production method
Physicochemical properties and material characterisation	Composition or purity, solubility, size distribution, aspect ratio, shape, specific surface area, agglomeration or aggregation, density, pH, crystalline phase, surface chemistry, dustiness, porosity, photocatalytic activity, radical formation potential
Environmental fate and behaviour†	Stability, biodegradation, bioaccumulation, transport and distribution
Environmental toxicology†	Aquatic toxicity, soil macroorganism and microorganism toxicity
Mammalian toxicology†	Pharmacokinetics (adsorption, distribution, metabolism, excretion), acute toxicity, irritation, sensitisation, genotoxicity, specific organ system toxicity (reproductive, neurological, immunological, cardiovascular), chronic toxicity
Material safety	Flammability, explosivity, incompatibility

Source: Organization for Economic Cooperation and Development, OECD.^{9,10} CAS, Chemical Abstracts Service; EC, European Commission.

*. See OECD^{9,10,11} for the complete list of measures.

†. These are listed under section '1.3 End points' in the OECD report.¹⁰



Source: US National Research Council.^{12,13}

FIGURE 1: The health risk assessment paradigm.

For example, some physicochemical properties identified are chemical composition, particle and fibre geometry and dimensions, biopersistence, surface activity and dose (as particle surface area, number, mass or volume). Mechanisms elucidated in particle and fibre toxicity include oxidative stress and persistent inflammation.⁶ It is therefore envisaged that similar mechanisms may be applicable to the potential toxicity of ENMs.

With the help of expert groups, a number of international agencies have proposed specific *in-vitro* and *in-vivo* tests to assess the toxicity of ENMs.¹⁰ *In-vitro* assays are considered useful for screening and prioritising substances for *in-vivo* studies. Such assays may also be useful in the elucidation of the mechanistic pathways involved in the toxicity of nanomaterials, which may need further validation with *in-vivo* studies. Some recent studies have shown progress in correlating acute *in-vivo* and *in-vitro* responses in hazard identification,⁶ which suggest that *in-vitro* assays could be used to reduce animal testing in the initial hazard evaluation of ENMs.

Internal dose estimation is important in the prediction of the biological effect at the target tissue (based on absorption, distribution, metabolism, and elimination processes). Although data still are limited, the role of physicochemical properties on the systemic distribution of some ENMs, including AuNP, has been studied. *In-vivo* studies have shown that the primary site of gold (and silver) accumulation is the liver,¹⁷ and that this process of accumulation is influenced by particle size, surface charge and route of exposure.¹⁸ For

example, in a rat intratracheal instillation study of two sizes of AuNP, the pulmonary and systemic toxicity responses were similar for both particle sizes at the dose tested, and there was no clear relationship between toxicity and particle size or agglomeration state.¹⁹ A subchronic inhalation study of exposure to AuNP in rats showed no adverse effects in rats exposed to the two lower doses, but rats exposed to the highest dose showed reduced lung function and inflammatory changes in their lung tissue.²⁰ Further studies are needed to assess the hazards of AuNP, although *in-vivo* and *in-vitro* studies suggest that particle size and charge can influence the fate of gold nanoparticles in the body. For other materials, particle shape also influences the ability of inhaled particles to translocate from the lungs and be retained in the pleural tissue. Such kinetic information can be used to identify the nanomaterial characteristics with the greatest potential to be hazardous and to design nanomaterials with safer properties (e.g. lower biopersistence).²¹

Dose-response assessment

The next step of the risk assessment process is the dose-response assessment, in which the quantitative relationship between the dose and a toxic response is determined. This assessment is typically performed using animal models, from which an equivalent human dose (often for a specific population, such as workers or the general public) is estimated.¹²

The aim of this step is to identify the doses at which certain toxicity end points (i.e. effect levels) occur. These end points can include acute and chronic toxicity, immunotoxicity,



neurotoxicity, mutagenicity, reproductive or developmental toxicity, and carcinogenicity. Another aim of this step is to identify the effect level, such as the 'no observed adverse effect level' (NOAEL) or the 'lowest observed adverse effect level' (LOAEL). Non-cancer risk assessment using a NOAEL or LOAEL approach assumes a threshold mechanism such that exposures below the threshold are not expected to cause harmful effects. The most sensitive end point is typically selected and extrapolated to humans by adjusting for differences across species (e.g. body weight and metabolic rate). The human-equivalent effect level is then divided by a series of uncertainty factors to determine a reasonably safe exposure level. Uncertainty factors are typically those that account for a less than or equal to 10-fold difference caused by species differences, animal vs. human response, human inter-individual variability, use of a LOAEL instead of a NOAEL and use of subchronic rather than chronic dose-response data. Examples of regulatory levels derived using this approach include inhalation reference concentrations (RfC), oral reference doses (RfD) and acceptable daily intakes (ADI).²² Alternatively, risk-based effect levels can be estimated from statistical modelling of the dose-response data and low-dose extrapolation from the 95% lower confidence limit estimate (i.e. the benchmark dose limit, BMDL) of the benchmark dose (BMD). The BMDL is used to account for variability in the data and to provide confidence that the true BMD is greater than the BMDL. The US National Research Council risk assessment guidelines recommend a greater emphasis on risk-based approaches to decision-making, such as in the development of exposure limits and reference concentrations.¹³

There are two major issues that are of concern when establishing the dose-response relationship of ENMs. Firstly, challenges exist in the measurement of nanoparticles at target deposition sites and their biopersistence at those sites. A number of physicochemical properties, including their surface functional groups and dissolution of surface ions, may influence their distribution to these sites.²³ Secondly, the establishment of the most biologically relevant dose metric for nanoparticles (mass, volume, number or surface area) poses a further challenge in the establishment of a dose-response relationship for ENMs.²⁴ Particle volume or surface area, rather than mass, have been shown to better describe the overloading of lung clearance and the resulting inflammation response in rats.^{25,26} A recent study has concluded that no single dosimetric parameter of particles – mass, surface area or number – will be universally applicable to all nanomaterials. Hence, the selection of the best dose metric for toxicity testing and the risk assessment of specific ENMs will remain a challenge.²⁷ Toxicity studies can help to reduce this challenge by providing standard measures of physicochemical properties at toxicity to facilitate hypothesis testing across groups of ENMs.

Exposure assessment

Obviously, there is no risk to health from a hazardous agent if there is no exposure to that agent. Exposure assessment

identifies the exposure of a population to a contaminant, and includes the route, magnitude, duration and timing of the exposure.¹²

Exposure assessment may cover medical administration through intradermal, intraperitoneal and intravenous injections.²⁸ Exposure may also be in the form of inhalation, ingestion and dermal absorption in occupational settings. In addition, exposure through the general environment, the fate and transport of the substance, as well as the points of entry into the environment or through the use of consumer items, should be considered.

Adequate exposure assessment cannot be conducted without sufficient information on the sources of exposure, the amount exposed to and the routes of exposure. Exposure via inhalation is possible for airborne nanomaterials; exposure via the gastrointestinal tract is possible because of the increasing number of applications of ENMs in food packaging and food products. Workers are at risk from dermal exposure to ENMs during the manufacture of ENMs. Workers and the general public are also at risk from dermal exposure to ENMs through the manufacture and use of textiles and cosmetics such as sunscreens. Because of lack of data on ENMs in the aquatic or terrestrial environment,²⁹ it is even more challenging to estimate exposure of the general population or the environment to ENMs. Once again, the unique physicochemical properties of nanomaterials may determine their behaviour in different environments and therefore their frequency or patterns of exposure.

Finally, exposure varies on the basis of conditions such as the manner in which materials are handled in the workplace, the way in which ENMs partition to various phases (e.g. water and air), and the mobility and persistence of ENMs in each of these phases, and the magnitude of the sources (e.g. production volume or size of markets). Exposure scenarios for the identified ENMs should therefore be developed throughout their life cycles to address key questions and gaps in the risk assessments of the identified ENMs. It may be likely that when an ENM is embedded in polymers or in other materials, the potential for exposure is minimal,³⁰ but this potential may change during the processing or recycling of the material, or as it enters a waste stream. In this instance, the life-cycle concept propagated by the Environmental Protection Agency should also be considered for the risk assessment of nanoparticles.³¹

Risk characterisation

The final step in risk assessment is risk characterisation, in which data obtained during hazard identification, dose-response assessment and exposure assessment are integrated, and the uncertainty in these estimates is evaluated.¹³

The paucity of data for many ENMs with regard to workplace exposure levels and hazard potential are key sources of



uncertainty in the risk characterisation of these ENMs. There is also uncertainty about the potential novel or enhanced effects of certain ENMs as a result of their small size and their ability to interact with cells and cell organelles via mechanisms related to nanoscale properties. Additional uncertainties include the influence of the route of exposure (e.g. inhalation via air, ingestion via food or water or intravenous via medical treatment) on internal dose and toxicity; the role of particle size (e.g. agglomerated versus dispersed); the mechanisms involved in the uptake and fate of ENMs in the body; and the persistence or degradation of ENMs in the environment. A full life-cycle risk characterisation would include not only the risk assessment of workers at the site of production, but also a risk assessment along the life cycle of the ENMs, including their transport, use and disposal.^{31,32}

The research efforts to address these questions are by nature multidisciplinary. Best work practice calls for greater exposure control and caution when there is increased uncertainty about potential adverse health effects.³³ In the absence of information on specific ENMs, the scientific literature on substances with analogous physicochemical properties could be used to derive initial estimates of the hazard and the target level of exposure control.³

Examples of risk assessments and exposure limits for nanomaterials

The occupational exposure limits (OELs) currently proposed for ENMs are based on animal data, as human health effects data are not available for specific ENMs. The US National Institute of Occupational Safety and Health used quantitative risk assessment methods similar to those used for other airborne, poorly soluble particles³⁴ as the basis for developing draft OELs for ultrafine (of nanometre diameter) and fine (of micrometre diameter) TiO₂.³⁵ Epidemiology studies of workers who handle TiO₂ have generally shown no increase in the risk for lung cancer. Chronic inhalation studies in rats, however, have shown an increase in the risk for lung tumours; this risk is associated with the particle surface area dose of TiO₂ and other poorly soluble particles in the lungs.^{35,36} Subchronic inhalation studies have shown that pulmonary inflammation is also associated with the particle surface area dose in the lungs of rats and mice. Because ultrafine TiO₂ has a greater surface area per unit mass than fine TiO₂, a lower mass dose of ultrafine TiO₂ than that of fine TiO₂ was associated with lung inflammation and tumours. These findings of adverse lung effects being associated with the particle size or surface area provided the health basis for the two OELs proposed for fine and ultrafine (or nano) TiO₂: 0.3 mg/m³ for ultrafine TiO₂ and 2.4 mg/m³ for fine TiO₂ (8-h time-weighted average concentrations).³⁵

Several research groups recently have proposed specific OELs for carbon nanotubes (CNTs): 50 µg/m³,³⁷ 30 µg/m³,³⁸ 7 µg/m³,³⁹ 1–2 µg/m³.⁴⁰ These proposed OELs are 8-h time-weighted average concentrations and were derived from animal studies in which lung inflammation or fibrotic responses were exhibited after subchronic or short-term exposure to different types of CNTs. Most of these risk

assessments used data from subchronic inhalation studies of multiwalled CNTs in rats, in which 0.1 mg/m³ was the NOAEL in one study³⁸ and a LOAEL in a study of a different type of multiwalled CNT.⁴¹ Another risk assessment used data from a 4-week inhalation study in rats, in which the LOAEL was 0.37 mg/m³.³⁷

Although these examples show progress in the development of proposed OELs for ENMs, the number of different types of nanoparticles being developed and used in commercial products is outpacing efforts to develop OELs in the workplace. Reasons for this shortcoming include limited data on both the hazards of and the exposure to ENMs, for example, in workplaces.⁴² Challenges in the measurement of exposure include the current inability of the available online monitoring technologies to separate the ubiquitous background nanomaterials from the ENMs; limitations in the sensitivity of some analytical methods for detecting and quantifying exposures to nanoparticles in the workplace³⁹; and the lack of consensus on the metrics and methods to be used for exposure measurement.^{4,16} Thus, new approaches are needed to better characterise potential hazards.

The concept of developing exposure limits for categories of ENMs with similar physicochemical properties – and well-characterised biological effects for representative ‘benchmark’ particles in each group – may be one approach to setting exposure limits for different types of nanomaterials.³ The British Standards Institute proposed four categories of ENMs and associated ‘benchmark exposure levels’, which were described as pragmatic guidance levels.² A four-category approach was also adopted by the Institut für Arbeitsschutz⁴³ in Germany. Standardised toxicity testing procedures and risk assessment methods are also needed for global harmonisation of health and safety practices for ENMs.^{10,32}

Nanomaterials currently synthesised in South Africa

With the realisation of the importance of nanotechnology, and the foresight and leadership of the DST, centres dedicated to the research and development of nanotechnology have been established to research the synthesis and applications of nanomaterials.⁴⁴ Tertiary institutions (the universities of the Witwatersrand, Cape Town, Tshwane, Johannesburg, Stellenbosch, Western Cape, Zululand, KwaZulu-Natal, Limpopo and Rhodes) and research centres (the Council for Scientific and Industrial Research, MINTEK and iThemba Laboratory for Accelerator Based Sciences) in South Africa are presently actively involved in the synthesis and application of nanomaterials. Nanomaterials that are currently being investigated at these centres range from metal and metal oxide particles to CNTs and nanocomposites, and thus represent some of the major categories of ENMs being developed and used worldwide (Table 3). A few examples of these activities, by no means an exhaustive list, are summarised below as an indication of the diversity of nanomaterials investigated in South Africa.



AuNPs are being investigated for use in catalysis,⁴⁵ in the purification of air at room temperature⁴⁶ and in molecular diagnostics.⁴⁷ Almost every university and research centre is in some way involved with the synthesis or application of CNTs. The application of CNTs in catalysis⁴⁸ and their use in the removal of hexavalent chromium from industrial wastes⁴⁹ have been reported. These ENMs are also being studied for their potential to cheaply and efficiently treat water in order to meet drinking, industrial and environmental water quality standards.⁵⁰

In South Africa, quantum dots and their application in diagnostics, security systems, biological probes and optics are being investigated.⁵¹ A great variety of nanocomposites is also being synthesised, including CNTs, polymers, quantum dots and metallic-based nanoparticles such as silicon and TiO₂.⁵² Finally, the preparation of magnetite nanoparticles, using a variety of synthesis methodologies,⁵³ with anticipated applications for effluent processing, therapeutic and diagnostic testing and densimetric separation, is being undertaken.

The complexity of understanding the potential exposure and toxicity of so many variations of ENMs is illustrated by the variety of compositions and applications. Determining which materials are most likely to result in exposure, prioritising materials for specific testing, and determining to what extent physicochemical properties can be used to infer hazard, are some of the challenges in the risk assessment of ENMs. Protecting researchers and workers who are producing and using these materials is paramount, starting from the research laboratory and production line to the use of these materials in various applications.

Challenges in health risk assessment: Relevance to South Africa

The general consensus is that considerable work remains to be done to generate the required data for ensuring appropriate risk evaluation of ENMs. These data may include the characterisation of the wide range of nanomaterials being produced and information on their complex behaviours in different media. Because of the diversity of ENMs, toxicity is specific to a tested nanomaterial and cannot be generalised or extrapolated, even within the same chemical family. Not much is known about the dose–response curves and toxicological modes of action of specific nanomaterials and how these materials might enter the body. Once inside the cell, the data needed for specific ENMs, such as toxicity and carcinogenicity, adsorption, distribution, metabolism and excretion, as well as occupational and environmental monitoring information, is largely unavailable. Moreover, longer-term effects of ENM need urgently to be addressed. Generalised exposure scenarios have also not been developed for ENMs for risk assessment along the life cycle of an ENM.⁴ Without reliable data on effects and exposure, in-depth risk assessments of ENMs for developing risk-based management strategies or regulations cannot be conducted.

There is no methodical data available on nanomaterial production levels, on exposure scenarios in working environments or research laboratories, or on exposures related to consumer products. Not much is known about emissions from nanomaterial production facilities and the fates of these emissions in the environment. In the absence of adequate data, extra precautions in controlling exposure to ENMs are recommended.³³

TABLE 3: List of nanotechnology-associated activities and materials in South African tertiary and scientific institutions.

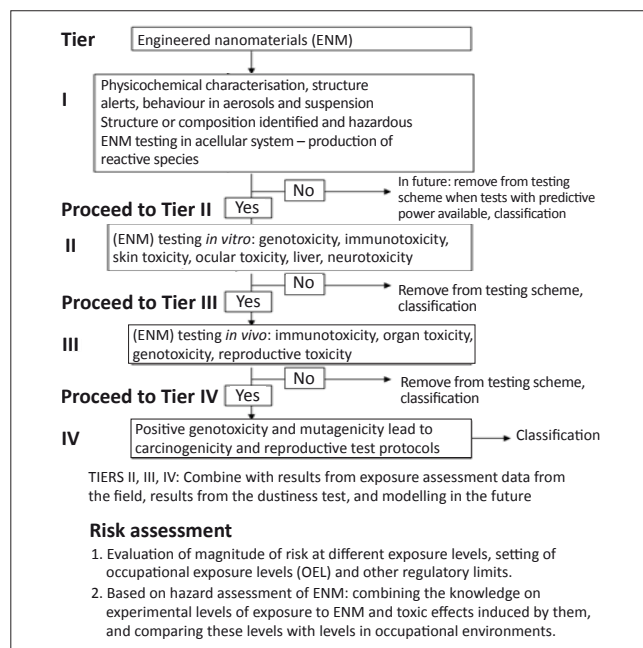
Category	Institution	Research or activity focus
Tertiary institutions	Rhodes University	Gold nanofibres, carbon nanotubes, quantum dots, nanostructured metallophthalocyanines, sensor detectors development
	Tshwane University of Technology	Nanocomposites – silver nanoparticles mounted on different substrates, functionalised single-walled carbon nanotubes
	University of Cape Town	Cobalt, gold, titanium dioxide and silicon nanoparticles; dendrimers
	University of Johannesburg	Bimetallic nanoparticles – nickel on iron – supported on functionalised carbon nanotubes and then co-polymerised with β -cyclodextrin
	University of KwaZulu-Natal	Novel polyelectrolyte carboxymethyl konjac glucomannan-chitosan, multiwalled carbon nanotubes
	University of Limpopo	Modelling tools to investigate the properties of nanomaterials
	Stellenbosch University	Magnetite, nanofibres of different polymers (e.g. cellulose acetate, nylon, polyacrylonitrile, polyvinyl alcohol), nanoparticles of various forms, carbon nanotubes, single-walled carbon nanotubes
	University of the Western Cape	Immunosensor – aflatoxin B ₁ -bovine serum albumin conjugate on a polythionine or gold nanoparticle-modified glassy carbon electrode, nickel microwire arrays, carbon nanopipes
	University of the Witwatersrand	Metal nanoparticles (gold, silver, copper, palladium), polymers, carbon nanotubes
	University of Zululand	Quantum dots (CdS, InS, InSe, PbS, HgS and ZnS), nanocomposites Au–CdSe
Science councils and research centres	MINTEK	Gold in catalysis for the oxidation of carbon monoxide to carbon dioxide, molecular diagnostics, metal–polymer composites
	Council for Scientific and Industrial Research	Nanocomposites, metal nanoparticles (e.g. silicon, TiO ₂ , ZnO, SnO ₂), quantum dots, nano-biotech, carbon nanotubes, polymers
	iThemba Laboratory for Accelerator Based Sciences	Carbon nanotubes, nanoparticle composites (silver, palladium, copper), polyaniline encapsulated gold nanoparticle composite, gold–vanadium dioxide nanocomposite, quantum dots



The development of a risk assessment for ENMs in South Africa is fraught with similar challenges as those experienced internationally. ENMs synthesised in many countries, including South Africa, encompass a multitude of classes, which contain different subclasses and countless modified versions. Their diversity makes it unfeasible to conduct an *ad-hoc* risk assessment of every type of nanoparticle. Thus the development of risk assessment strategies based on categories of ENMs (e.g. based on mode of action) is needed.³ For ENMs to present a risk there must be both a potential for exposure and a hazard from such exposure. Prioritisation strategies for toxicity testing and risk assessment therefore consider which ENMs have the most commercial production and exposure potential⁵⁴; these priority ENMs may also vary by country.

Exposure and response data obtained from animals or humans, as well as information on sources of exposure and the physicochemical properties of the ENMs along their life cycle are required for those ENMs identified as high priority for a comprehensive risk assessment. A tiered toxicity testing approach, that provides reliable and predictive evidence of ENM-related toxicity or safety would be extremely important to support the appropriate testing of safety and toxicity of these materials.^{4,10} Such an approach would allow one to separate materials of concern from those of lesser or no concern. Linkov and collaborators⁵⁵ have developed a decision tree approach that incorporates tiered toxicity testing strategies. Another more comprehensive tiered testing strategy for ENMs has recently been proposed⁵⁶ (Figure 2). The key issue in these approaches is well-defined decision points at which testing can be stopped or continued in a subsequent, more resource-intensive tier. Toxicity testing of ENMs should be initiated with a careful physicochemical characterisation of the materials (Figure 2), including the use of reference materials currently available as dispersions, especially for *in-vitro* studies.⁵⁷

These well-characterised ENMs can then be further investigated in the next tier by first using acellular systems to explore the reactivity of the materials, before exploration at a subcellular level. It would then be possible to proceed to *in-vitro* cellular models that would support evidence-based testing processes.⁵⁸ Such *in-vitro* testing methods should address carefully chosen and relevant end points shown to be predictive of human toxicity.⁵⁹ Positive and consistent results from validated *in-vitro* tests with demonstrated predictive power would lead to higher tier testing procedures with experimental animals. The advantages of this tiered system is that these lower tier tests would be short-term studies, and although long-term studies with experimental animals would be required, these would be less frequently required than is the case today. A major challenge for the development of this kind of tiered testing procedure continues to be the validation of *in-vitro* tests with appropriate predictive power for *in-vivo* effects in whole organisms, although some progress has been shown for prediction of acute lung effects from *in-vitro* data.^{6,60}



Source: Savolainen et al.⁵⁶

FIGURE 2: Proposal for toxicity testing strategy for engineered nanomaterials.

Summary and conclusion

Risk assessment is the process of determining whether exposure to a substance will lead to negative health effects. A comprehensive risk assessment of ENMs will therefore involve evaluation of the exposure potential, the hazardous properties and the dose–response relationship of ENMs. These findings could then be used to characterise the risk and to provide information for risk-based decision-making, such as establishing exposure limits and other risk management measures to protect human health and the environment – the ultimate goal of the risk assessment exercise.

For a resource-limited country such as South Africa, it is essential that best practice guidelines developed internationally be adopted and that research be conducted as a priority to provide the data needed for risk assessments specific to the situation in South Africa.

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Competing interests

We declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

Authors' contributions

M.G. was the project leader and wrote the first draft of the article. E.D.K. and K.S. contributed sections as per their expertise in risk assessment and assisted in finalising the article.



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