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Need For Nanotoxicological Assessment - A Review

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ABSTRACT: The novel characteristics specific to nanomaterials have led to many new applications. The property of NMs is unique as they differ significantly from their microcrystalline counterpart. These properties offer great opportunities for the development of new industrial applications increasing their worldwide distribution. Widescale commercial exploitation also enhances the likelihood of their environmental and human exposure. In this regard, nanotoxicology and nano-risk have been attracting the increasing attention of toxicologists and regulatory scientists, particularly in relation to the unique properties of NPs that may render them potentially more dangerous than their micro-sized counterpart and may cause unexpected adverse health effects to exposed people However, there are also concerns arising on the potential health and environmental impacts of such nanomaterials. There are several pathways that includes air, water and land borne pathways leading to exposure of such nanomaterials to living systems. Therefore, it is articulated that prerequisite of nanotoxicological assessment is the need of the hour. This review provides international status on studies relating to nanotoxicological assessment and factors of nano-bio interactions within biological systems.
KEYWORDS Microcrystal, Nanomaterials, Nanotoxicology, Pathway

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I. INTRODUCTION

Nanotechnology is a contemporary area of research dealing with objects with at least one of their dimensions in order of a few hundreds of nanometers. Most widely accepted definition of nanotechnology to date appears on the NASA website: "the creation of functional materials, devices and systems through control of matter on nanometer length scale (1–100 nm), and exploitation of novel phenomena and properties (physical, chemical, biological, mechanical or electrical) at this scale". The novel characteristics specific to nanomaterials have led to many exciting new applications, they also raise concerns about potential health and environmental impacts. Despite recent advances in medical and toxicological research, it is still unclear as to how nanomaterials interact with biological entities and which parameters of nanomaterials drive these responses. To achieve this goal, health and environmental effects of nanomaterials must be known, necessitating toxicity studies. Reports on nanotoxicity have shown significant levels of toxicity associated with various nanoparticles (NPs). Due to lack of safety information and regulations available to materials chemists, workers who synthesize nanomaterials are constantly exposed to these nanomaterials without knowing adverse health effects.

The property of NPs are unique as they differ significantly from their microcrystalline counterpart. These properties offer great opportunities for development of new industrial applications increasing their worldwide distribution. Widescale commercial exploitation also enhanced the likelihood of environmental and human exposure (STOA 2008). In this regard, nanotoxicology and nano-risk has attracted increased attention of toxicologists and regulatory scientists, particularly in relation to unique properties of NPs that may render potentially more dangerous than their micro-sized counterpart and may cause unexpected adverse health effects to exposed people. This review in general articulates on occupational health and safety aspects of NPs mainly in understanding their interaction mechanisms with the biosystems.

II. ULTRAFINE VERSUS NPS

Ultrafine particle pollution has been an unavoidable by-product of industrial revolution and it received enormous attention due to its adverse effects on human health. The dangerous effects on inhaling fine particles of silica and asbestos are well known. Although NPs show innumerous beneficial properties that promote their commercial exploitation, they can also pose health risks. Today, engineered NMs (ENM) are used in several consumer and industrial products including sustainable energy, healthcare, automobiles, information and communication, cosmetics and food products. In addition, it is expected that there will be an immense increase in the number of consumer products relying on nanotechnology in future. Researchers

forecast that manufactured NPs may become suspended in the air during fabrication, distribution, use and disposal and pose threat to the environment (Oberdörster *et al*., 2007).

III. NANOTOXICITY

Nanotoxicology still nascent subject seeking data for safer application. Research on occupational hazard associated with application of NPs have shown association of particulate air pollution with respiratory conditions such as asthma, lung cancer and cardiovascular conditions like myocardial infarction (Dockery, 2009). Greater emphasis must be provided to completely understand the biological properties of NPs including uptake, distribution, intracellular trajectory, interactions with subcellular system and biomolecules (Asharani *et al*., 2012). However, it should also be taken into consideration that the properties of NMs vary within same elemental type based on size, shape and surface functionalization. Nanotoxicology studies should include the risk assessment throughout the entire life cycle of NMs commencing from synthesis to application to their waste management (Fig.1).

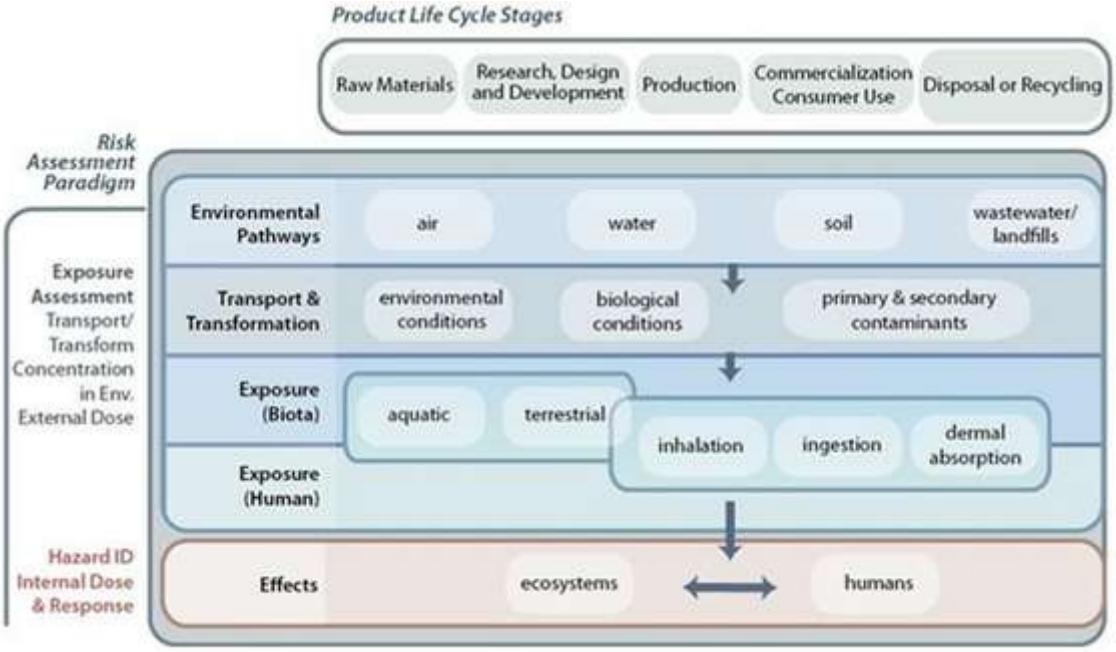

Fig.1: The risk assessment paradigm integrated with NM life cycle stages – (*across top*). – Larry Gibbs 2017. (Design credit: N.R. Fuller of Sayo-Art.)

Toxicological studies can help to mitigate the risks from undesired exposure of NMs by formulating and regulating suitable handling, packaging procedures, and restrictive applications. There are also questions about the safety of engineered NMs in consumer products, implantable medical devices, or to the environment after disposal. Because of these concerns, a new field of research termed as "nano (eco) toxicology" has emerged in the last decade. This field deals with the effect of engineered NPs on living organisms and the health and environmental issues related to the use of engineered NMs. Due to increasing use of synthetic NPs, an increase in the introduction of such particles into environmental media, i.e. soil, water and air, must be expected soon. Studies involving naturally formed ultrafine particulates or those produced by combustion throws concern over the behaviour and impact of NPs on environment. Broad applicability of nanotechnology and great differences existing between the various NMs require a differentiated evaluation of possible risks for the environment and human health.

NPs, by their high surface activity can behave like free radicals. A free radical is any chemical species that is capable of independent existence possessing one or more unpaired electron in the outer (valence) shell of the molecule (Halliwell and Gutteridge,1989). The key factor is the structure of these species (Halliwell 1995) and the reason for its high reactivity. ROS is a collective term referred to describe oxygen radicals and certain non-radicals that are either oxidizing species or that can easily have converted into radicals.

IV. ADME OF NMS

The biological life cycle of NMs including absorption, distribution, metabolism, excretion (ADME)

in fishes has been reviewed extensively by many researchers. For traditional chemicals, target organs are often identified by measuring the contaminant of interest in the tissues (Fig.3). This is problematic for NMs because reproducible, reliable methods for detecting NMs in tissues are still under development. For metal-based NPs, it may be possible to measure total metal concentrations in tissues (e.g. tissue Ti levels for rainbow trout *Oncorhynchus mykiss*, exposed to nanoparticles; Federici *et al*., (2007). For NMs added to the water, the gills of aquatic organisms would be directly exposed. The translocation of intact NMs, or NPs, across the gills is yet to be unequivocally demonstrated. However, coherent anti-Stokes Raman scattering (CARS) microscopy indicates that some metal NPs may be located both on and inside gill epithelial cells of fishes (Johnston *et al*., 2010). Gill injury from NPs has been observed. For example, the exposure to SWCNT increased the ventilation rate of *Oncorhynchus mykiss* and the gill irritation caused some secretion of mucus with gill pathology (Smith *et al*., 2007). Damage to the gill of zebrafish exposed to 1·5 mg^{-1} Cu NPs for 48 h was characterized by proliferation of epithelial cells and edema (Griffitt *et al.*, 2007). These effects on the gill are also well known for many other chemicals (Mallat, *et al.*, 1985), but there may also be some nano-related gill injury. The gill injuries observed with NMs do not necessarily cause major haematological disturbances. Several authorshave reported normal haematology without evidence of red cell swelling or changes in plasma Na^{+} (Federici *et al*., 2007; Smith *et al.*, 2007). There are some significant knowledge gaps in understanding the respiratory effects of NMs, with only a few materials and species being tested. Studies of the effects of water chemistry (pH, hardness, dissolved oxygen, etc.) on ecotoxicity are yet to be completed.

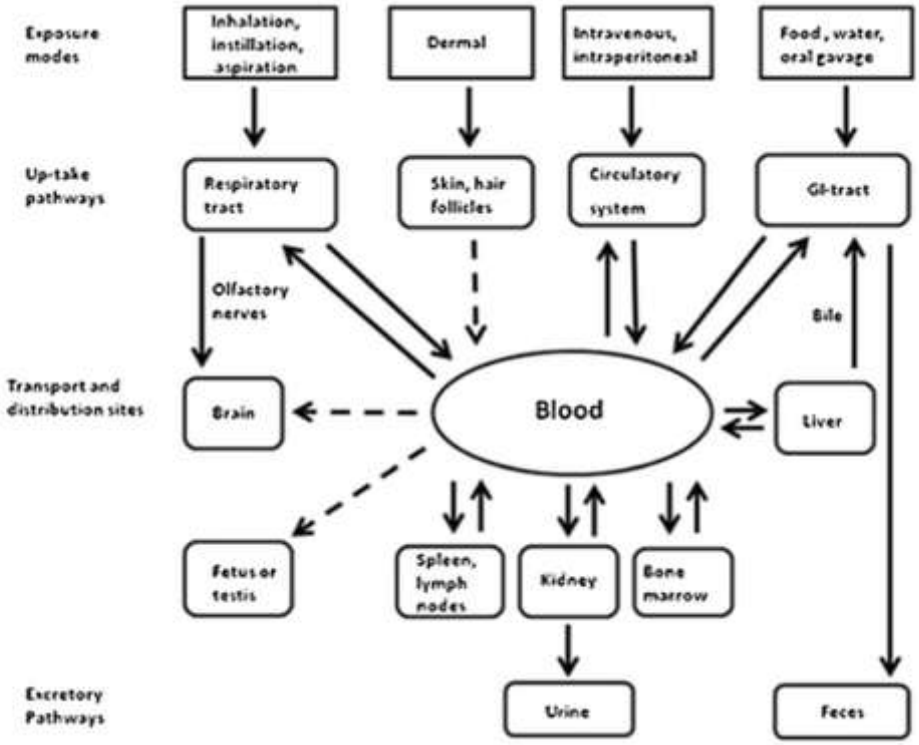

Fig 2 Toxicokinetics of NMs distribution within the biological system- Liu et al., 2013.

From the view point of environmental risk assessment, information on dietary uptake rates, the trophic transfer of NMs and the chronic effects of NMs on growth are of interest. Ramsden *et al* ,(2009) reports, no effects on the growth of *Oncorhynchus mykiss* with inclusions of up to 100 mg kg 1 of TiO_2 NPs, but also reports elusiv e biochemical disturbances to oxidative stress markers, $Na^{+}K^{+}$-ATPase and electrolytes with higher concentrations. Studies have shown the transfer of NMs from the water to sediment surfaces, and into aquatic food chains (Bradford *et al*., 2009), suggesting that fishes are likely to receive dietary NM exposure in the field via the food chain. However, it is still early in research, and detailed studies confirming the amounts and mechanisms of NM uptake across the gut of aquatic species are needed.

V. CHARACTERISTICS OF NMS AFFECTING THEIR FUNCTIONALITY AND BIO-INTERACTION

Many parameters like geometric size, phase purity and environment influence the nature and extent of interactions of the NPs with the ecosystem, as shown in figure 3. This again alters their nanotoxicology

behaviouor, calling for a detailed research on the nano-bio interactions for each given set of parameters studied. For example, the addition of functional groups to the surface of NPs plays a vital role in determining enhanced activity of ions leading to toxic potential. In calf thymus DNA was found to be dependent on the intensity of UVA radiation and the concentration of nanoparticles in the exposure media (Wamer *et al.,* 1997). In rainbow trout gonadal tissue cells, the presence of UV radiation in combination with nanoparticles was found to significantly increase toxicity and the number of DNA strand breaks compared proportionately to volume fraction of nanoparticles (Veevers and Jha, 2008).

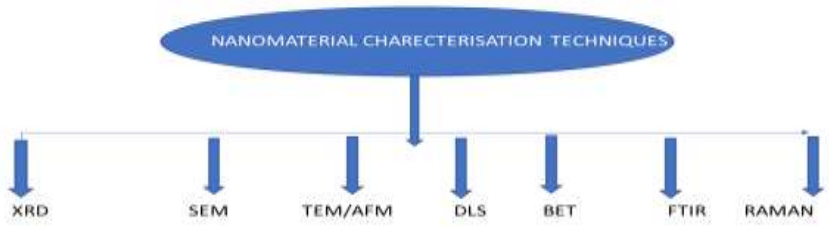

Fig. 3 Characteristic features of NPs that influence their functionality.

V. i. Size and surface area

Materials manufactured at the nano-scale, have properties that differ from their "bulk sized" equivalents, often due to their large surface area to volume ratio. Although in one study larger intratracheally instilled nanoparticles particles were found to be more toxic in mice (Grassian *et al.,* 2007), inhalation studies in other rodents and *in vitro* studies have in general indicated that smaller NPs generate greater inflammatory responses than larger ones (Brown *et al.,* 2001; Inoue *et al.,* 2009; Singh *et al.,* 2004). Though size and surface area are related, size may however not be an accurate dose pattern. Instillation studies in mouse and rat models have shown that though smaller sized NPs cause a greater inflammatory response than larger sized particles on a mass basis, the level of inflammatory response is dependent on the total surface area of particles instilled (Brown *et al*., 2001; Oberdörster, *et al*.,2000; Stoeger *et al*., 2006; Yamamoto *et al*., 2006).

V. ii. Shape

The shape of the particle may also play an important role in determining the toxicity. Cytotoxicity studies on a murine macrophage cell line tested with a range of different NPs types using crysotile asbestos as a positive control, found that carbon nanotube aggregates had a very similar cytotoxicity index to asbestos. Soto *et al.* (2005) suggested that the proximity in toxicity may be due to the physical similarities between the two particle types. A similar study also found that the injury caused to plasma membranes of mouse macrophages by MWCNTs was corresponding to damage caused by asbestos (Hirano *et al.,* 2008). *In vivo* studies have shown that mice exposed to MWCNTs *via* inhalation and intraperitoneal injection can cause asbestos-like pathogenic responses (Poland *et al.,* 2008) and induction of mesothelioma (Takagi *et al.,* 2008) and granulomas (Warheit *et al.,* 2004).

V. iii. Photochemistry

The presence of ultraviolet light may also influence the toxicity of some NPs. Several metal oxide NPs including titania and ZnO exhibit photocatalytic activity when exposed to light and as a result can generate ROS in aquatic media. Genotoxic effects of UV-illuminated nanoparticles have also been reported. 2008The hydroxylation of guanine bases have also been reported in calf thymus DNA was found to be dependent on the intensity of UVA radiation and the concentration of nanotitania in the exposure media (Wamer *et al.,* 1997).

Exposure Routes and Limits of Nanoparticles

Human exposure to nanoparticles may occur during both manufacture and use. Nanoparticles can be encountered as aerosols, suspensions or emulsions. The major routes of exposure that have toxicological relevance in the workplace are inhalation and dermal exposure. It is reported that more than 150 items of "manufacturer identified nanotechnology-based consumer products would have long term dermal contact". The most common NMs found in consumer products for dermal application, are also widely used for toothpaste, food colorants and nutritional supplements. Therefore, oral exposure may occur during production or use of such products. A Study by Weir *et al.* (2011), report that candies, sweets and chewing gums contain the highest

amount of n a n o titanium dioxide on a scale of <100 nm. In nanomedicine, intravenous or subcutaneous injection of nano particulate carriers is a unique way of delivery into the human body. Among applications, where samples of metallic nanopowders embedded into products such as household paint, they have been shown to be less harmful.

V iv Toxicokinetics

Toxicokinetics describes the rate at which a substance enters the body through different routes of exposure and the subsequent modification that it undergoes after entering the body (Fig.1). The level or concentration of nanoparticles in the body system depends on the rate (or kinetic) of absorption, distribution, metabolism, and excretion of nanoparticles. These processes may occur after exposure through inhalation, ingestion, dermal contact, and intraperitoneal or intravenous injection. Acute toxicity of nanoparticles have been frequently studied in rat and mouse models with multiple exposure routes of administration. The number of studies targeting the respiratory system outweighs the other exposure routes. Studies on exposing the pulmonary system to nanoparticles showed both local and systemic symptoms with aggravation of pre-existing symptoms. Nanoparticles administered through the lung is more inflammatory than its bulk counter part of similar chemistry at equal mass concentrations. However, on an equal particle surface area basis, pulmonary inflammation to nanoparticles was like that of the bulk counterpart. Results from the other exposure routes cannot be ignored. For example, research evidence demonstrates that nanoparticles can be absorbed through the lung or GIT into the systemic circulation and then distributed in different organs such as the liver, kidneys, spleen and brain. Distribution and accumulation of these particles in the organs could induce organ injuries and inflammatory responses. However, in most of these conditions, the doses employed are too high to be practically feasible. Researchers concluded that the signaling pathway of liver injury in the nanoparticles-stimulated mouse liver might occur sequentially via activation of TLRs → NIK → IκBkinase→ NF-κB → TNF-α → inflammation → apoptosis → liver injury (Warheit *et al.*, 2007).

Animal and human epidemiological data have led nanoparticles to be designated as "possibly carcinogenic" to humans as per the IARC 2006 report. Surprisingly, few studies have investigated carcinogenicity of nanoparticles, and only recently, NIOSH (2011) concluded that inhaled ultrafine to nanoparticles is a potential occupational carcinogen. The most relevant data for assessing the health risk for workers are results from a chronic animal inhalation study performed by Heinrich *et al*. (1995), in which rats exposed by inhalation to nanoparticles showed increased rates of adenocarcinomas compared to controls. Interestingly, in this study, mice exposed to the same particle, according to the same methodology, did not show differences in tumour rates compared to controls. Aside from demonstrating that nanoparticles can induce lung cancer in exposed animals, an interesting finding of this work is the difference in carcinogenicity between rats and mice. The species difference in response to insoluble and low toxicity dust, and the controversial approach to classify such a dust as a potential human carcinogen is subject to debate. Moreover, NIOSH has concluded that nanoparticles is not a direct-acting carcinogen but acts through a secondary genotoxic mechanism primarily related to particle size and surface area, as supported by the comprehensive analysis of the data reported by Heinrich *et al.* (2002) and those obtained by Lee *et al.* (1985) with fine-sized NPs. However, the toxicological profile of nanoparticles has not been completely understood and several concerns have emerged on the potentially undesirable effects of these nano-properties about the harmful interactions with biological systems based on environment reports (Nel *et al.,* 2006). The recently recognized occupational carcinogenic potential of the inhaled nanoparticles have enhanced these scientific concerns. Therefore, an appropriate assessment of the risks for the general and occupational exposed seems necessary as per Cho *et al.* (2010).

VI. CONCLUSION

Concerns regarding potential risk of genetic disorders, particularly for people occupationally exposed to high doses of NPs. Size and therefore surface area have influence on the toxicity of NPs.Thus, further research is necessary to fully understand molecular toxico-potential effects and to determine the conditions in which they occur to fully evaluate on exposure hazard as distinctive nanotoxicological research. The dose-response relationship and accretion of NPs requires special attention considering that traditional mass dose that does not well reflect the biologically effective dose of NPs. Other dose metrics, such as surface area combined with surface reactivity or particle number and bioaccumulation should be evaluated as ulterior, as they may be better, descriptors of the hazard potential to cause damage at the site of particle deposition are far from scientific inevitability assessment. The foremost significance for meticulous research in nanotoxicology is to establish a safety paradigm on day today application of nanoparticles.

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