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Risk Evaluation and Exposure Hazards of Engineered Nanomaterials: A Survey

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ABSTRACT: *The particles at the nanoscale take on completely new physical properties, making their potential dangers to humans and environment mostly unknown. Considering the theory and practice of using nanoparticles, nanotechnology has a great potential, but not limited to improving treatment of various disorders and in vitro diagnostics. However, there is not much data available on the toxicity of nanoparticles in relation to human health. There need to be more information regarding the toxicology of new nanomaterials and how they should be handled in the contexts of industry, consumers and environment. Adoption of best practices to minimize exposure and hazards from engineered nanomaterials has become the need of hour. In this paper, a unique set of detailed survey is gathered and analyzed, establishing baseline data for future studies and as a first step towards developing safe handling guidelines for nanomaterials. In this survey, the known facts about nanomaterial hazards are summarised, the potential entry points of different classes of nanoparticles into the human body are discussed, their likely pathways inside the body are explored and published experimental results on the bioactivity of nanomaterials are analysed.This work will give researchers a better understanding of current practices in the nanotechnology industry, valuable insight into current information gaps that might exist in understanding and managing the health implications of this revolutionary technology and future directions of research.*

Keywords: *Carbon nanotubes, engineered nanomaterials, nanotoxicology, dendrimers, quantum dots.*

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I. INTRODUCTION

When GOD plays around at the nanoscale, HE changed the rules of game. And human being starts to take this advantage from god's favor, to use the particular properties of nanostructures in applications of manufacturing of new materials for medicine, industry, recreation and environment [1]. The term nanoparticle (NP) is used to describe a wide variety of materials of submicron size. An internationally acknowledged definition for nanoparticles does not exist. It is used differently, based on the context of material being described. According to a recent definition suggested by British Standards Institution "Nanoparticles are the particles with one or more dimensions at the nanoscale". They have defined the nanoscale as dimensions of the order of 100 nm or less. At this size, the substance's physical, chemical and biological properties frequently are different from what they were at the micrometer and larger scales. By harnessing these new properties, researchers have found that they can develop materials, devices and systems that are superior to those, in use today. As with practically all scientific breakthroughs, nanotechnology carries both risks and rewards. While it appears almost certain that the rewards will greatly outweigh the risks, attention must be paid to possible dangers to the well-being of humans from this new technology. Science at the nanoscale involves a change of perspective [2]. The properties of materials can be different on a nanoscale for two main reasons. First, nanomaterials have, relatively, a larger surface area than the same mass of material produced in a larger form. This can make materials more chemically reactive (in some cases materials that are inert in their larger form are reactive when produced in their nanoscale form), and affect their strength or electrical properties. Second, below 50 nm, the laws of classical physics give way to quantum effects, aggravating optical, electrical and magnetic

behaviours different from those of the same material at a larger scale. These effects can give materials very useful physical properties such as exceptional electrical conductance or resistance, or a high capacity for storing or transferring heat, and can even modify biological properties, with silver for example becoming a bactericide on a nanoscale. These properties, however, can be very difficult to control. For example, if nanoparticles touch each other, they can fuse, losing both their shape and those special properties—such as the magnetism—that scientists hope to exploit for a new generation of microelectronic devices and sensors. On a nanoscale, chemistry, physics, biology, electronics, materials science, and engineering start to converge and the distinctions as to which property a particular discipline measures no longer apply. All these disciplines contribute to understanding and exploiting the possibilities offered by nanotechnology, but if the basic science is converging, the potential applications are infinitely varied, encompassing everything from tennis rackets to medicines to entirely new energy systems. This twin dynamic of convergent science and multiplying applications means that nanotechnology's biggest impacts may arise from unexpected combinations of previously separate aspects, just as the internet came about through the convergence of telephony and computing. The following section outlines the properties of three of the most talked-about nanotechnologies: carbon nanotubes, nanoparticles, and quantum dots.

The earliest known use of nanoparticles is in the ninth century during the Abbasid dynasty [3]. Arab potters used nanoparticles in their glazes so that objects would change colour depending on the viewing angle (the so-called polychrome lustre). Today's nanotechnology, i.e. the planned manipulation of materials and properties on a nanoscale, exploits the interaction of three technological streams: new and improved control of the size and manipulation of nanoscale building blocks, new and improved characterisation of materials on a nanoscale (such as spatial resolution, chemical sensitivity etc.) and new and improved understanding of the relationships between nanostructure and properties and how these can be engineered. Nanotechnology has a great potential in improving treatment of various disorders and in vitro diagnostics. However, there is not much information available on the toxicity of nanoparticles in relation to human health. The use of conventional practices for handling nanomaterials appears to shoot from a lack of information on the toxicological properties of nanomaterials, as well as nascent regulatory guidance regarding the proper environmental, health and safety practices that should be used with them. Engineered nanomaterials (ENMs) are intentionally designed to take advantage of properties that emerge at the nanoscale, and nanotech workers typically face the greatest exposure risks from engineered nanomaterials. For example, in products containing nanomaterials that are incorporated in a plastic composite or other solid matrix, risks to consumers are believed to be minimal because the materials are locked up tight. But workers who make the products, and who handle the nanomaterials in raw form, face more risk of exposure.

Toxic effect of nanomaterials on humans is the primary concern of the health industry. Nanomaterials are able to cross biological membranes and access cells, tissues and organs that larger-sized particles normally cannot. Nanomaterials can gain access to the blood stream via inhalation or ingestion. This may lead to both genotoxicity and biochemical toxicity. A recent study suggests that inhaled carbon NPs are capable of rapid translocation into the circulation [4]. On the contrary, a conflicting report suggests that inhaled carbon NPs remain within the lung up to 6 h after inhalation, without passing to systemic circulation [5]. In a recent study [6], suitability of mouse spermatogonial stem cell line as a model system to assess nanotoxicity was evaluated in the male germline in vitro. As nanomaterial-based products enter the market, there is an urgent need for related research in order to prevent dramatic consequences of any health-oriented issues caused by nanotechnology-driven products. Recent research has brought to light, concerns over the safety of use of nanomaterials and also the long-term adverse effect of their use. Hence it is essential for us to establish the toxicity, safety and risks involved in the usage of these nanoparticles. In this survey, we try to show which types, sizes and concentrations of nanoparticles are safe for human use and this will help in developing diagnostic, prognostic and therapeutic models using nanoparticles. The organization of the paper is as follows: Section 2 deals with nanotoxicology, a sub-specialty of particle toxicology. It addresses the toxicology of nanoparticles which appear to have toxicity effects that are unusual and not seen with larger particles. Section 3 describes the different classes of nanoparticles and their toxicity. Engineering controls for reducing ENM exposure is discussed in Section 4 and Concluding remarks are presented in Section 5.

II. NANOTOXICOLOGY

The smaller a particle, the greater it's surface area to volume ratio and the higher its chemical reactivity and biological activity. Because of their large surface area, nanoparticles will immediately adsorb onto their surface some of the macromolecules they encounter on exposure to tissue and fluids. This may, for instance, affect the regulatory mechanisms of enzymes and other proteins. Genotoxicity [7] describes a deleterious action on a cell's genetic material affecting its integrity. Genotoxic substances are known to be potentially mutagenic or carcinogenic, specifically those capable of causing genetic mutation. Genotoxins may be lethal and could

cause various metabolic and developmental abnormalities. This can be passed on to following generations as well. As discussed, the specific physical, chemical and biological properties make nanoparticles as potent molecules for diagnostics and therapeutics in modern medicine. Nanoparticles are widely used because of their desirable properties in industrial, medical and cosmetic fields. These particles can be released into the human environment and then can be inhaled. Most exposure to airborne nanomaterials occurs in the work place. The extremely small size of nanomaterials also means that they readily gain entry into the human body than larger sized particles. The behaviour of these nanoparticles inside the body is still a major question that needs to be answered.

There are several reviews addressing nanotoxicology aspects; however, they are intended for a narrow, specialized audience. Several are comparatively general [8] while others address selected aspects of nanoparticle toxicology, such as epidemiological reviews of exposure to particles and health affects [9]; targeted drug delivery; particle characterization methods; [10] screening strategies and future directions of research; and regulation of nanomaterials. While the tremendous positive impacts of nanotechnology are widely publicized, potential threats or risks to human health and the environment are just beginning to emerge. With limited information available for support, critics are presenting a number of concerns on the devastating effects of nanotoxicity on human health and the environment. Detailed studies on the long-term effects of NPs are the need of the hour to overcome or reduce possible threats. Simultaneous agglomeration, sedimentation and diffusion at physiologically relevant concentrations should be taken into account while conducting quantitative studies on the uptake of NPs into biological systems, to assess the corresponding risks on human health.

III. TOXICITY OF DIFFERENT CLASSES OF NANOPARTICLES

3.1 Carbon Based Materials

These nanomaterials are composed mostly of carbon, commonly taking the form of a hollow spheres, ellipsoids, or tubes. Spherical and ellipsoidal carbon nanomaterials are referred to as fullerenes, while cylindrical ones are called nanotubes. These particles have many potential applications, including improved films and coatings, stronger and lighter materials, and applications in electronics. *Carbon nanotubes* (CNTs; also known as buckytubes) are allotropes of carbon with a cylindrical nanostructure. These cylindrical carbon molecules have novel properties that make them potentially useful in many applications in nanotechnology. Determining the toxicity of carbon nanotubes has been one of the most pressing questions in nanotechnology. Unfortunately such research has only just begun and the data are still fragmentary and subject to criticism. Under some conditions, nanotubes can cross membrane barriers [11], which suggest that if raw materials reach the organs they can induce harmful effects such as inflammatory and fibrotic reactions.The toxicology issues relating to carbon nanotubes (CNTs), may be examined in this section. CNTs are discussed here exclusively as an inhalation hazard. Global revenues from CNT in 2006 are estimated at ~ $230 million with a growth rate of ~ 170% [12]. This provides potential for workplace and even eventual general exposure, if there is attrition of materials that contain them. Concern has been raised over the safety of CNT because they have three properties that are clearly associated with pathogenicity in particles.

1. They are nanoparticles and so could have more toxicity than larger sized particles.
2. They are fiber-shaped and so might behave like asbestos and other pathogenic fibers which have toxicity associated with their needle-like shape.
3. They are essentially graphitic and so are expected to be biologically biopersistent.

3.2 Metal Based Materials

These nanomaterials include quantum dots, nanogold, nanosilver and metal oxides, such as titanium dioxide. A quantum dot is a closely packed semiconductor crystal comprised of hundreds or thousands of atoms, and whose size is on the order of a few nanometers to a few hundred nanometers. Changing the size of quantum dots changes their optical properties. Quantum dots are nanoparticles made of semiconductor materials with fluorescent properties. Crucial for biological applications quantum dots must be covered with other materials allowing dispersion and preventing leaking of the toxic heavy metals [13]. *Colloidal Gold*, also known as *"nanogold"*, is a suspension of sub-micrometre-sized particles of gold in a fluid - usually water. The liquid is usually either an intense red colour (for particles less than 100 nm), or a dirty yellowish colour (for larger particles) [14]. In recent days gold nanoparticles (GNPs) are widely using in all the fields, particularly in medicine. The toxicity of GNPs has been investigated at the cellular level. GNPs enter cells in a size and shape-dependent manner [15, 16]. Uptake of GNPs reaches a maximum when the size nears 50 nm and when the aspect ratio approaches unity. The transport efficiency reaches a plateau 30 min after incubation. The uptake of GNPs is consistent with receptor-mediated endocytosis. Nevertheless, most GNPs can enter cells efficiently, and

most studies indicate that they are nearly harmless to cultured cells [17].Gold nanoparticles may not affect cell viability in short-term but may affect cell proliferation and cause DNA damage. Its mechanism of action and involvement are yet to be revealed. Currently gold nanoparticles (Au NPs) are used in different biomedical applications, such as intracellular gene regulation [18], chemotherapy [19] and drug delivery [20], as well as in optical and electronic applications. A previous study revealed that gold-silica nanoshells release significant heat when exposed to near-infrared (NIR) light (650–950 nm) and have been used to produce thermal cytotoxicity in vitro [21]. Unfortunately, this treatment approach is automatically limited to use in superficial malignant tumors because of the minimal tissue penetration (< 2–3 cm depth) by NIR wavelength light. However, the gold-silica nanoshell study demonstrated that nanogold has potential clinical use as a thermal conductor of non-invasive energy sources. Gold, like most metals, is an excellent conductor of electrical and thermal energy.

Silver nanoparticles are used as antibacterial or antifungal agents in a diverse range of applications: air sanitizer sprays, pillows, slippers, socks, face masks, wet wipes, soap, shampoo, detergent, toothpaste, air filters, coatings of refrigerators, washing machines, food storage containers, vacuum cleaners and even in cellular phones. Ingestion of Ag can cause argyria, the benign condition characterized by the bluish-graying of the skin that occurs through the preferential deposition of Ag in the basal lamina of soft tissues such as the skin, liver, and spleen[29] and blood vessels, gastrointestinal tract, liver, and kidney [22].

Titanium dioxide (TiO_2) particles with diameter larger than 100 nm are considered biologically inert in both humans and animals [23]. Based on this understanding, titanium dioxide nanoparticles have been widely used in many products, such as white pigment, food colorant, sunscreens, and cosmetic creams. However, adverse effects of TiO_2 nanoparticles have recently been uncovered [24]. New research is exploring the potential use of nanostructured TiO_2 photocatalyst materials for sterilizing equipment of environmental microorganisms in the health care facility [25].

Exposure to nano-titanium dioxide showed DNA and chromosome damage to a degree linked to all the big killers, namely cancer, heart disease, neurological disease and aging [26]. Warheit and co-workers recently dosed the lungs of rats with 3 sizes of titanium dioxide nanoparticles and suggested that toxicity is not dependent upon particle size or surface area. A clear conclusion regarding particle size could not be reached as only 3 sizes were tested, of which one was of a different crystal phase, and the two of the same crystal phase (rutile) were of different shapes (rods, ~200 nm × 40 nm, and dots, ~10-20 nm). In a follow up study, these authors tested the pulmonary toxicity of 3 sizes (hydrodynamic diameter: 136 nm, 149 nm and 382 nm) of the rutile phase with alumina surface coating, and compared it to 25 nm TiO2 particles (of a different crystal phase). In a third study, they examined the toxic potential of 3 samples of different crystal phases, however, the sizes were also different [27]. Surface properties were proposed to account for the differences in biological responses. Oberdörsteret.al. [28, 29] conducted pulmonary toxicity tests with 20 nm (80% anatase) and 250 nm (100% anatase) titanium dioxide particles and found that the total surface area was a metric that related to neutrophil lung inflammation in rats. No clear trends with regard to the influence of TiO_2 crystallinity and particle size on biological activity could be seen in these different studies and contrasting concepts were proposed. One major reason was the paucity of different well-characterized TiO_2 samples (in terms of size and crystallinity) that were used, thus precluding the development of convincing conclusions about the function of parameters such as particle size or crystal phase.

3.3 Dendrimers

These nanomaterials are nanosized polymers built from branched units. The surface of a dendrimer has numerous chain ends, which can be tailored to perform specific chemical functions. This property could also be useful for catalysis. Also, because three-dimensional dendrimers contain interior cavities into which other molecules could be placed, they may be useful for drug delivery. *Polymers* such as polysaccharide chitosan nanoparticles have been used for some time now as drug delivery systems. Recently, water-soluble polymer hybrid constructs have been developed. These are polymer–protein conjugates or polymer–drug conjugates. Polymer conjugation to proteins reduces immunogenicity, prolongs plasma half-life and enhances protein stability. Polymer–drug conjugation promotes tumour targeting through the enhanced permeability and retention effect and, at the cellular level following endocytic capture, allows lysosomotropic drug delivery [30]. Fig 1 may be referred for the diseases associated with nanoparticle exposure. Table 1 gives the involvement of nanoparticles toxicity in various pathways.

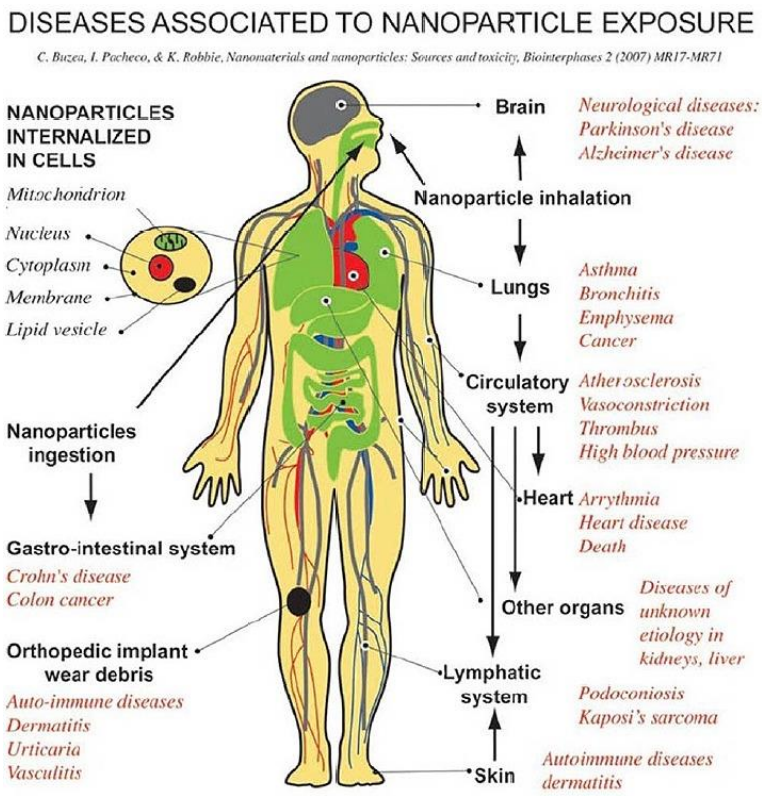

Fig. 1 Diseases associated with nanoparticle exposure [30]

Table 1: Involvement of Nanoparticles Toxicity in Various Pathways [30].

Membrane damage / leakage / thinning	Cationic NPs
Protein binding/unfolding responses/loss of function/fibrillation	TiO2, Carbon NPS
DNA cleavage and mutation	Ag NPs
Mitochondrial damage: electron transfer/ATP/Apoptosis	Ag and Gold NPs
Lysosomal damage: proton pump activity/lysis/frustrated phagocytosis	Ag, Gold NPs and Carbon Nanotubes (CNTs)
Inflammation: signaling cascade/cytokines/chemokines/adhesion	Metal Oxide NPs (eg. TiO2) and CNTs
Fibrogenesis and tissue remodeling injury	CNTs
Blood platelet, vascular endothelial and clotting abnormalities	SiO2
Oxidative stress injury, radical production, GSH (Glutathione) depletion, lipid peroxidation, membrane oxidation, protein oxidation.	CNTs, Metal Oxide NPs, Cationic NPs

In 1990, the lipid nanoparticles were invented in the laboratories, the first patent filings took place in 1991. The lipid nanoparticles were developed as alternative to traditional carriers such as polymeric nanoparticles and leptosomes [31]. Meanwhile many research groups are active worldwide, their results are reviewed which cover many different administration routes: dermal and mucosal, oral, intravenous/parenteral, pulmonary but also ocular (Fig 1, Table 1). The lipid nanoparticles are also used for peptide/protein delivery, in gene therapy and various miscellaneous applications (e.g. vaccines) [32, 33, 34]. Although lipid nanoparticles represent potent drug carriers, for many formulations toxicity data are rare. *Liposomes* are nanoparticles comprising lipid bilayer membranes surrounding an aqueous interior. The amphilic molecules used for the preparation of these compounds have similarities with biological membranes and have been used for improving the efficacy and safety of different drugs [35]. Usually, liposomes are classified into three categories on the basis of their size and lamellarity (number of bilayers): small unilamellar vesicles or oligolamellar, large unilamellar vesicles and multilamellar vesicles. The active compound can be located either in the aqueous spaces, if it is water-soluble, or in the lipid membrane, if it is lipid-soluble. Recently, a new generation of liposomes called 'stealth liposomes' have been developed. Stealth liposomes have the ability to evade the interception by the immune systems, and therefore, have longer half-life [36].

3.4 Cellular interaction with nanoparticles

Like nanoorganisms (viruses), nanoparticles are able to enter cells and interact with subcellular structures. Cellular uptake, subcellular localization, and ability to catalyze oxidative products depend on nanoparticle chemistry, size, and shape [6]. The mechanism by which nanoparticles penetrate cells without specific receptors on their outer surface is assumed to be a passive uptake or adhesive interaction. This uptake may be initiated by Vander Waals forces, electrostatic charges, steric interactions, or interfacial tension effects, and does not result in the formation of vesicles [37, 38]. (Steric interactions occur when nanoparticles have molecules with size, geometries, bonding, and charges optimized for the interaction with the receptors). After this type of uptake, the nanoparticles are not necessarily located within a phagosome (which offers some protection to the rest of the cellular organelles from the chemical interaction with the nanoparticle). For example, C60 molecules enter cells and can be found along the nuclear membrane and within the nucleus. Very small nanoparticles, such as C60 molecules with a diameter of 0.7 nm, are able to penetrate cells via a different mechanism than phagocytosis, probably through ion channels or via pores in the cell membrane [39]. This type of uptake and free movement within the cell makes them very dangerous by having direct access to cytoplasm proteins and organelles. Uptake location is likely to depend on material type; however, current research does not provide sufficient information to drawing conclusions on this subject. Upon nonphagocytic uptake, nano-particles can be found in various locations inside the cell, such as the outer-cell membrane, cytoplasm, mitochondria, lipid vesicles, along the nuclear membrane, or within the nucleus [40]. Depending on their localization inside the cell, the nanoparticles can damage organelles or DNA, or ultimately cause cell death. Recent studies have used a composite phenotype (psychosis) that includes BPD, SCZ, psychosis not otherwise specified, and schizoaffective disorder, to identify shared susceptibility loci. Several chromosomal regions are reported to be shared between these syndromes (18p, 6q, 10p, 13q, 22q) [41].

3.5 Biomarkers to assay the toxicity

With very few exceptions, previous nanotoxicity studies implicitly involved the assumption that the techniques developed for risk assessment of hazardous chemical substances can be applied in unchanged form to explore cell response in nanoparticle laden media. This misleading approach has the consequence that the actual dose of exposure is ill defined or, more often, completely unknown [34]. Pro-inflammatory cytokines such as interleukin- 6 (IL-6) and tumor necrosis factor alpha (TNF- alpha) are involved in the formation of toxic peroxynitrite by increasing the activity of nitric oxide synthase (NOS) enzyme. Nitric oxide (NO) is potent inflammatory mediator because of its strong reactivity with oxygen, superoxide and iron-containing compounds. Prostaglandins are well known as proinflammatory mediators, and inhibition of cyclooxygenase (COX) has long been used in the management of inflammation. Levels of prostaglandin E2 (PGE2) are increased in various states of inflammation. Unlike larger particles, nanomaterials may be taken up by cell mitochondria and the cell nucleus. Studies demonstrate the potential for nanomaterials to cause DNA mutation and induce major structural damage to mitochondria, even resulting in cell death. Size is therefore a key factor in determining the potential toxicity of a particle. The greater chemical reactivity of nanomaterials results in increased production of reactive oxygen species (ROS), including free radicals and it is one of the primary mechanisms of nanoparticle toxicity; it may result in oxidative stress, inflammatory cytokines production and consequent damage to proteins, membranes, DNA and cell death [8]. Humanized NPs, termed nano-proresolving medicines, are mimetics of endogenous resolving mechanisms, possess potent beneficial bioactions, can reduce nanotoxicity, and offer new therapeutic approaches [42].

Hazard Assessment from Fire and Explosion of ENMs

Some ENMs have very high reactivity for catalytic reactions, thus raising the possibility of fire and/or explosion. As particle size decreases and surface area increases, the ease of ignition and the likelihood of a dust explosion increase. It may create a second hazard due to increased ENM release. There are no reports that ENMs have been used intentionally, e.g. by terrorists, or unintentionally to cause fires, explosions, or an airborne obscurant effect.

IV. ENGINEERING CONTROLS

ENM exposure can be reduced through the use of engineering controls, such as process changes, material containment, and enclosures operating at negative pressure compared to the worker's breathing zone; worker isolation; separated rooms; the use of robots; and local exhaust ventilation (LEV). Given the lack of occupational exposure standards to provide guidance, the most prudent approach is to minimize exposure. A survey found that engineering controls in Switzerland were more commonly used in the production of powder than liquid ENMs. For the former, the use of PPE (masks, gloves, safety glasses, or full protective suits) was the

norm, although used by only ~16, 19, 19, and 8% of the workers, respectively [43]. This low use of PPE is thought to reflect the early stage of development of the ENM industry. It is anticipated that as this industry matures and knowledge is gained, control will more commonly include superior methods in the hierarchy of exposure control [44]. An international survey of ENM industry managers conducted in 2009-2010 by the University of California Center for Environmental Implications of Nanotechnology that focused on industry controls of ENM exposure, use of PPE, environmental risks, and perceptions revealed that 46% of the companies had a nano-specific environmental health and safety program, compared to 58% in a 2006 survey [45]. Some companies (a minority) were using inappropriate occupational environmental clean-up methods, such as sweeping and compressed air [46]. These results suggest more widespread adoption of nano-specific environmental health and safety programs and the use of PPE in the absence of superior controls are appropriate.

4.1 Process Containment

Process/source enclosure (i.e., isolating the ENM from the worker) can be aided by glove boxes, chemical fume hoods, biological safety cabinets (BSC), or an externally-vented LEV system. However, one should also consider that these methods can release ENMs into the environment, potentially creating environmental pollution and loss of costly material.

4.2 Local Exhaust Ventilation (LEV)

Air-displacement ventilation in an industrial setting was accomplished by introduction of supply air that entered at low velocity at the floor level and was cooler than room air. As the air rose it became warmer and was exhausted close to the ceiling. This provided efficient clearing of ENMs from the breathing zone [47]. A well-designed exhaust ventilation system with a HEPA filter should effectively capture airborne nanoparticles. A "down flow" booth, "elephant trunk", or fume hood may not provide sufficient protection because they may cause turbulence, spinning the ENM out of the airflow [48]. The effectiveness of engineering controls in ENM production and research facilities has been demonstrated in a few cases. Prior to use of engineering-control measures, total airborne mass concentrations of MWCNTs, measured by area sampling, were 0.21 to 0.43 mg/m^3 in a laboratory research facility where the powders were blended to formulate composites. After enclosing and ventilating the blending equipment and re-locating another piece of equipment that produced considerable vibration, the concentration decreased to below the limit of detection [49]. In another study, the effectiveness of LEV was assessed during clean-out of slag and waste, which used brushes and scrapers, of reactors that produced 15 to 50 nm diameter ENMs. A portable LEV unit was used that had been shown to reduce welding fume exposure [50]. The reduction in release of 300- to 10,000-nm Ag, Co, and Mn particles during cleanout of reactors used to make nanoscale metal catalytic materials was 75, 94, and 96%, respectively [51]. These results illustrate the importance of good exhaust hood design as well as the worker protection provided by a BSC.

4.3 Administrative Controls

When engineering controls are not feasible for reducing exposure, administrative controls should be implemented. These are policies and procedures aimed at limiting worker exposure to a hazard [52]. These could include a nanoscale material hygiene plan; preparation, training in, and monitoring use of standard operating procedures; reduction of exposure time; modification of work practices; and good workplace and housekeeping practices. For example, one laboratory was thoroughly cleaned after high air concentrations of nanoscale materials were measured in a facility engaged in the commercial compounding of nanocomposites. A large decrease of airborne 30 to 100 nm particles resulted. Subsequent routine maintenance kept the particles below those originally observed, leading the authors to conclude that this administrative control was beneficial in reducing potential exposure. Biological monitoring and medical examination, a component of secondary prevention, is another administrative control [52].

4.4 Personal Protective Equipment

The last line of defence in the hierarchy of exposure control is the use of PPE, such as respirators, protective clothing, and gloves.

4.4.1 Respirators

Major types of respiratory protection include dust masks, filtering facepiece respirators, chemical cartridge/gas mask respirators, and powered air-purifying respirators. NIOSH classifies filter efficiency levels as Type 95, 99, and 100, which are 95, 99, and 99.7% efficient, respectively. The filter's resistance to oil is designated as N, R, and P; N (not resistant to oil), R (resistant to oil), and P (oil proof). Some industrial oils can

remove electrostatic charges from filter media, reducing filter efficiency. Efficiency of N filters is determined using 300-nm median aerodynamic, charge neutralized, NaCl particles at a flow rate of 85 l/min; R and P filters are tested with dioctyl phthalate oil. The European Standards (EN 143 and EN 149) rank filtering facepiece (FFP) respirators as FFP1, FFP2, and FFP3, which are 80, 94, and 99% efficient, respectively, indicated by CE (for Conformité Européene) on complying products. They are tested with non-neutralized NaCl at 95l/min. Particles > 100 nm are collected on filter media by two mechanisms:

1) inertial impaction in which air flow deviates around the fiber but large denser-than-air particles do not and impact the fiber due to their inertia, and

2) interception where the particle trajectory takes it within a particle radius of the fiber, which captures the particle. Airborne nanoparticles behave much like gas particles.

Particles < 100 nm are collected by diffusion. Charged particles are trapped by electrostatic attraction, which involves an electrically charged particle and an electrically charged (electret) fiber. Electret filters are constructed from charged fibers. This appears to be a significant mechanism for respirator trapping of ENMs [53]. Neutral particles that pass through a charged fiber can be polarized by the electric field, thereby inducing charge to the particle. In dry conditions, ENM penetration decreases with time. With continued use, however, ENM penetration through an electrostatic filter increases; this was suggested to be due to the humidity of exhalation. Soaking fiber filters in isopropanol removes electrostatic charge. Studies treating filtering facepiece respirators with isopropanol, and then drying them, showed increased penetration of particles > 30 nm [53], indicating electrostatic charge is a significant mechanism of fiber entrapment of ENMs above this size.

4.4.2 Gloves

An unpublished study reported in 2005 the interaction of alumina and organoclay ENMs with powder-free (natural rubber) latex, powder-free (synthetic latex) nitrile, and cotton gloves [54]. Scanning electron microscopy showed that latex and nitrile gloves exhibited micrometer-sized surface pores/intrinsic voids. Although these surface imperfections were not complete holes, they may serve as pathways for the penetration of nanoparticles under unfavorable conditions, such as stretching and tearing. Stretching the latex and nitrile gloves to 200% of their original size greatly increased the pores/intrinsic voids. The surface pores may be important if they collect nanoparticles and the user does not remove the gloves when going to another location, thereby transporting the ENMs. Not surprisingly, there were wider gaps between the fibers in cotton gloves. The authors pointed out that ENMs may be treated with special coatings to enhance their dispersion characteristics, which may alter their permeability through glove materials. This study, however, did not determine the penetration of ENMs through gloves. Nitrile, latex, and neoprene gloves prevented ~10 nm titania and platinum ENM penetration [55]. Double gloving has been suggested [54], which should reduce material penetration when there is glove perforation as well as dermal contamination when removing a contaminated outer glove. However, double gloving has not been shown to significantly decrease material penetration [56].

4.4.3 Biological monitoring and medical examination

Secondary prevention in the continuum of the prevention and heirarchy of exposure control includes biological monitoring and medical examination, the early detection of asymptomatic disease, and prompt intervention when the disease is preventable or more easily treatable [57]. Occupational health surveillance is the process by which information obtained from any activity in the continuum of prevention and heirarchy of exposure control is collected and used to support or alter what is done at a step higher in the heirarchy, as shown in the right upward pointing arrow and discussed in [58]. Occupational health surveillance is the ongoing systematic collection, analysis, and dissemination of exposure and health data on groups of workers for the purpose of early detection and injury. It includes hazard surveillence, the periodic identification of potentially hazardous practices or exposures in the workplace, assessing the extent to which they can be linked to workers, the effectiveness of controls, and the reliability of exposure measures. A goal is to help define effective elements of the risk management program for exposed workers. Occupational health surveillance also includes medical surveillance, which examines health status to determine whether an employee is able to perform essential job functions [59]. It is required when there is exposure to a specific workplace hazard (OSHA, 29 CFR 1910.1450). This is different than medical screening or monitoring, a form of medical surveillance designed to detect early signs of work-related illness by administering tests to apparently healthy persons to detect those with early stages of disease or those at risk of disease. NIOSH concluded: "Currently there is insufficient scientific and medical evidence to recommend the specifc medical screening of workers potentially exposed to engineered nanoparticles" [59].

4.4.4. Diagnosis, therapy and rehabilitation

The third level in the continuum of prevention and heirarchy of exposure control, tertiary prevention, includes diagnosis, therapy, and rehabilitation. Owing to the lack of documented episodes of ENM exposure in humans that have resulted in adverse outcome, there is little experience with treatments of ENM exposure. One example that illustrates clever application of the knowledge of ENM properties was the use of UV light to visualize and treat the accidental dermal exposure of a human to quantum dots suspended in solution [60].

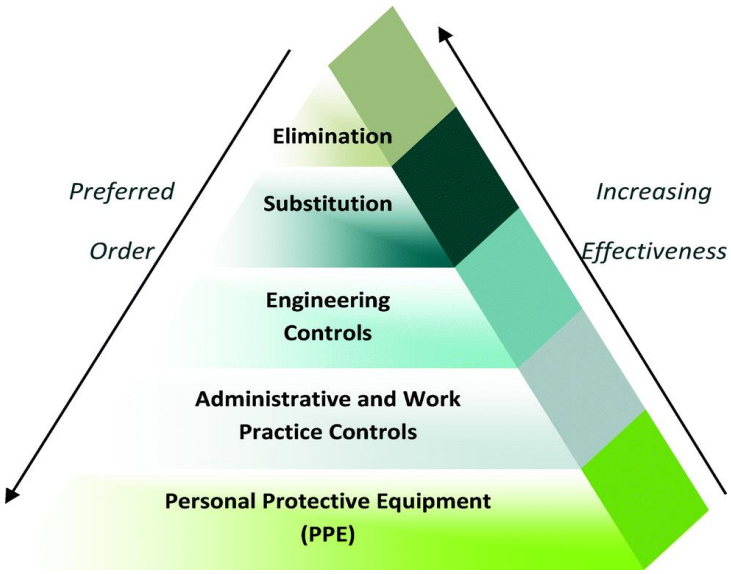

Fig.2 Evaluation of existing control measures

Clearly, further quantitative data is needed to fully assess the feasibility and cost-effectiveness of risk control options to prevent risks from exposure to ENMs. When there is little information on the efficiency of control measures specific to ENMs, the default efficiencies can be used for initial assessment purposes although it should not be considered exhaustive. Evaluation of existing control measures of exposure to ENMs is shown in Fig. 2 [61].

V. CONCLUSION

Nanotoxicology is an evolving new multidisciplinary field of science, and so there is a risk of change in its rapid development in the near future. The development of novel nanoparticles for pharmacology, therapeutics and diagnostics must proceed in tandem with assessment of any toxicological and environmental side effects of these particles. As the bioenvironment is already polluted with nano-particulates of particulate matter, caution should be taken to prevent and contain any environmental effects of intentionally generated nanomaterials. In this review we tried to put our effort to show the toxicity of various nanoparticles, which will be a very valuable reference source to students and investigators in this research field to guide them in their future work. There is no universal "nanoparticle" to fit all the cases, each nanomaterial should be treated individually when health risks are expected. The tests currently used to test the safety of materials should be applicable to identify hazardous nanoparticles. Proven otherwise, it would be a challenge for industry, legislators and risk assessors to construct a set of high throughput and low cost tests for nanoparticles without reducing the efficiency and reliability of the risk assessment. Nanoparticles designed for drug delivery or as food components need special attention. While the risk management of engineered nanomaterials (ENMs) receives significant attention, there is still a limited understanding of how to select optimal risk management measures (RMMs) for controlling and mitigating the risks associated with exposure to ENMs. Clearly, there exists a need to expand current risk management practices to ensure safe production, handling and use of ENMs. This paper has brought together the evidence on the adequacy of traditional controls to minimize potential health and environmental risks resulting from exposure to ENMs. The aim here is to advance our understanding of the risk management approaches relevant for ENMs, and ultimately to support the selection of the most suitable RMMs when handling ENMs. To that end, evaluative evidence collected from the review of relevant literature and survey of nanotechnology institutions are combined and summarised to understand the level of protection offered by each control measure, as well as the relative costs of their implementation. The findings suggest that most relevant

risk control options are based on isolating people from hazard through engineering measures or personal protective equipment (PPE), rather than eliminating hazard at source. Although control measures related to the modification of ENMs have high efficiency in the occupational risk control hierarchy, they are not widely employed since there is currently a high degree of uncertainty regarding the impact of manipulating nano-characteristics on the performance of final product. Lastly, despite its low cost, PPE is the least effective category in the occupational risk control hierarchy and should not be used on its own when significant risk reduction is required. Clearly, further quantitative data is needed to fully assess the feasibility and cost-effectiveness of risk control options to prevent risks from exposure to ENMs. When there is little information on the efficiency of control measures specific to ENMs, the default efficiencies can be used for initial assessment purposes although it should not be considered exhaustive.

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