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Toxicity of Nanomaterials and Recent Developments in Lung Disease

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1. Introduction

1.1 Background

Nanotechnology is the study of materials, compounds, devices, and/or systems at near atomic or molecular levels [1]. Usually, one of the dimensions of nanoproducts is between 1 nm and 100 nm length in scale. This emerging technology involves fabricating, imaging, measuring, modeling, and manipulating matter at this scale [2]. The goal of nanotechnology is to control individual atoms, molecules, or particles in order to significantly improve the physical, chemical, physicochemical, and biological properties of materials and devices for various humanitarian purposes. One of the most important aspects of nanotechnology is the greatly improved surface area-to-volume ratio at this level. It includes a broad range of highly multidisciplinary fields, such as engineering, materials science, colloidal science, physics, chemistry, pharmacy, medicine, and biology [3].

Nanomaterials can exhibit entirely different properties than their bulk-scaled conventional materials, enabling them to be appealing materials in many industrial applications [3]. For example, inert materials become catalytic materials (e.g., platinum and gold), opaque substances turn out to be transparent materials (e.g., carbon, copper), melting temperatures of solid materials are greatly reduced (e.g., gold, platinum, titanium), semiconductors become conductors (e.g., silicon, germanium), and non-combustible materials turn into combustible materials (e.g., aluminum) [1-3]. These fascinating behaviors of nanomaterials can be obtained only at nanoscale.

Nanomaterials, including nanoparticles, nanotubes, nanofibers, and nanocomposites, in the forms of metals and alloys, ceramics, polymers, and composites are all produced by nanotechnology processes and are considered to be the next generation of materials for manufacturing faster cars and planes, more powerful computers and satellites, more sensitive sensors, stronger materials for structural applications, and better micro- and nanochips and batteries [1]. This is because nanomaterials have outstanding mechanical, electrical, optical, magnetic, quantum mechanic, and thermal properties. Nanomaterials are already found in more than a thousand different products, including bacteria-free cloth, concrete, filtration units, sunscreen, car bumpers, tooth paste, polymeric coatings, solar and fuel cells, lithium-ion batteries, tennis rackets, wrinkle-resistant clothing, and optical, electronic, and sensing devices [2]. In the near future, the use of nanomaterials will

drastically increase worldwide. It is expected that the global market growth of nanotechnology is on track to reach one trillion dollars, and 50 percent of all new products will be nanotechnology-oriented by the year 2015 [20,21].

1.2 Motivation

Throughout the manufacturing, transportation, storage, consumption, and waste disposal of nanomaterials, the air, water, soil, and food (e.g., vegetables, fruits, and animal products) can become contaminated, resulting in countless public concerns [8,22]. Nanoparticles can also remain airborne for hundreds of kilometers and penetrate humans, animals, and plant cells, causing many known and unknown side effects [4]. Nanomaterials mainly enter the human body by inhalation, ingestion, and/or contact through skin and persist in the system. Most human-made nanomaterials do not appear in the environment, so living organisms may not have an appropriate immune system to deal with these nanoscale products [5,8]. Recent studies show that when some nanomaterials of varying surface areas, sizes, shapes, charges and energy, and compounds interact with human and animal cells or organs, they can damage or kill those cells or organs, block blood flow, and cause serious diseases [6,7]. Illnesses associated with nanomaterials include bronchitis, asthma, lung and liver cancer, Parkinson's disease, Alzheimer's disease, Crohn's disease, heart disease, and colon cancer [4,5]. Understanding the mechanisms and causes of nanomaterials will allow us to find efficient cures for lung diseases and other related illnesses associated with nanomaterials and devices [8,9].

Since nanomaterials are a new set of materials produced by entirely new manufacturing techniques, there are currently no specific rules and regulations for many of them. Hence, these uncertainties bring nanoethics and bioethics in research, development, and education to seek and examine the potential risks and rewards of the applications of these materials, as well as societal, economic, moral, health, and other broader human implications of advances in this technology [23-27].

Objectives of this study are as follows: *i*) to understand the surface properties of nanomaterials, *ii*) to determine the effects of nanoscale surfaces on the lung and other related diseases associated with nanomaterials, *iii*) to find possible protection methods for students, scientists, engineers, medical personnel, policymakers, and regulators working in the field, and *iv*) to inform these groups of people about progress and future developments in the field [4]. Some of these objectives and future developments are summarized below.

2. Surface properties of nanomaterials

Surface chemistry, surface potential, surface area, and particle size are dominating factors in the toxicity of nanomaterials [4-8]. These materials can react with the body, stay inert, and/or interact with a system based on their surface properties, and they can settle in the body for a long period of time [9-11]. It has been stated that almost all properties of nanoparticles are entirely different than their bulk-size counterparts [2]. Since the properties of nanomaterials are completely different, their toxicity could be different as well. Recent toxicological studies have demonstrated that particles less than 100 nm induce toxicity in many cell-cultured human and animal models [4-11]. Figure 1 shows the comparison of rat macrophage cells (raw cells) with different particles. As can be seen, nanoparticles are several orders of magnitude smaller than human and animal cells. They can be even smaller than DNA, pathogens, proteins, and enzymes [1]. Previous studies confirm that the smaller

the particle size, the higher the toxicity [8,14]. Note that human macrophages are approximately twice as large as rat macrophages, so nanoparticle penetration may be easier for human macrophages or other larger living entities.

The surface area of nanomaterials is exponentially high when the size is at nanoscale, so the surface chemistry (e.g., surface charge, zeta potential, and surface energy) of materials is drastically changed. The high surface area of nanomaterials means numerous unbonded atoms, resulting in huge surface interaction with surrounding tissues. Hence, surface chemistry can basically provide information about the mechanisms of biological toxicity of nanomaterials in cells [4,6]. For example, gold, silver, and platinum are chemically inactive and usually do not interact directly with the body at bulk scale. Allergic reactions and other toxic effects of these inert materials are at minimum level in bulk or at microscale. However, because of their size, the surface of nanoscale materials can be chemically activated to harm the surrounding cells or organs [4]. Some nanomaterials have higher surface-to-volume ratios, which can be also responsible for the shape-dependent surface reactivity and toxicity [12-17].

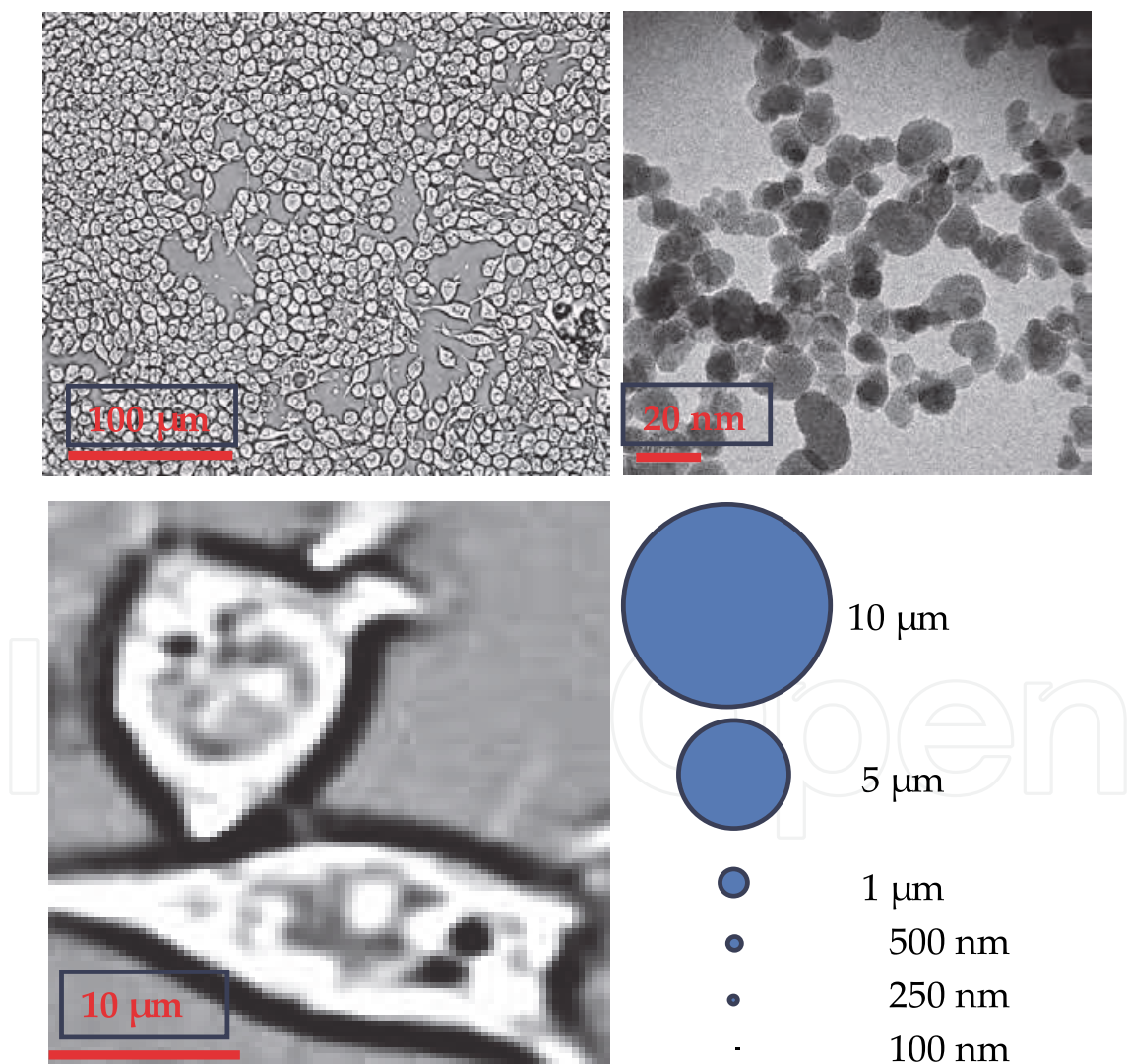


Fig. 1. Various images of cells and nanoparticles: A) rat raw cells (macrophages) at lower magnification, B) TEM image of magnetic nanoparticles with average diameter of 10 μm, C) comparison of raw macrophage cells, and D) drawings of particles at various size ranges.

Nanoparticles tend to aggregate due to intermolecular interactions, such as electrostatic, hydrophobic, and van der Waals, which makes the aggregation process easier [39]. Particle agglomeration, stability, and distribution can be related to surface charge and zeta potential values of nanoparticles in an aqueous media. The surface charge mainly regulates the stability of the nanoparticles [1]. At lower surface charges, nanoparticles usually agglomerate and make a larger cluster [2]. It has been reported that the toxicity of single particles is much higher than that of aggregated nanoparticles [4].

The toxicity of nanomaterials can be minimized using different chemical processes, such as surface treatment, modification, and functionalization [39-42]. In this way, surface energy and surface charge of nanoparticles can be changed via additions of chemicals (e.g., surfactants, electrolytes, and polymers). These chemicals include (but are not limited to) citric acid, tetramethyl ammonium hydroxide, gum Arabic, sodium dodecyl sulfate, and other carboxyl and amine functionalization groups. As a result, the surface functionalization process will help nanomaterials perform at less toxic levels in the body or in other applications [6,7].

3. Toxicity of nanomaterials and lung disease

Nanomaterials can enter the human body by various routes, such as breathing, eating, and touching the skin (Figure 2) [4-8,29,45]. Skin is the first defense barrier against the outside environment and is typically the first place on the body that is exposed to nanomaterial toxicity. Larger micron-scale particles normally cannot pass through skin and will not cause any health concerns. For the past few years, toxicological studies demonstrated that particles less than 100 nm in diameter induce toxicity in cell-cultured models as well as animal models [28-31]. It is also more difficult to remove nanoparticles from the body than the same kinds of larger particles. Table 1 shows the relationship between nanoparticle size and possible toxicity to living cells [8]. As is known, several kinds of sicknesses can be expected from nanomaterials that accumulate in the body, including inflammation of the airways, bronchitis, asthma, emphysema, lung cancer, neurodegenerative diseases, cardiovascular effects, liver cancer, Parkinson's disease, Alzheimer's disease, Crohn's disease, heart disease, and colon cancer [4,40].

Unless functionalized, most nanomaterials are not stable in in-vitro conditions, so their stability is dependent on several factors, such as pH, ionic strength, solubility, thermodynamic feasibility, concentration, kinetic facility of electron transfers, and redox conditions of biological media [5]. The toxicity of nanomaterials can occur through three different mechanisms in the body: *i*) dissolution process of nanomaterials in biological media, *ii*) catalyst properties of nanomaterials, and *iii*) reduction and oxidation (Redox) evolution of the surfaces [4-6].

In one study, an organ exposed to nanoparticles was analyzed, and the results indicated that the smaller particles diffused into the respiratory system faster than microscale particles [5]. It was also found that nanoparticles penetrate into cells and, by transcytosis, across epithelial and endothelial cells and into lymph circulation to reach very sensitive parts of the body, such as the nervous system, bone marrow, brain, lymph nodes, spleen, and heart. This study concluded that surface coating and in-vivo surface modification could reduce the side effects of those nanoparticles [6,7]. Figure 3 shows the nanoparticles of a lead compound and scanning transmission electrograph of ceria nanoparticles exposed to clearing sludge [29,45].

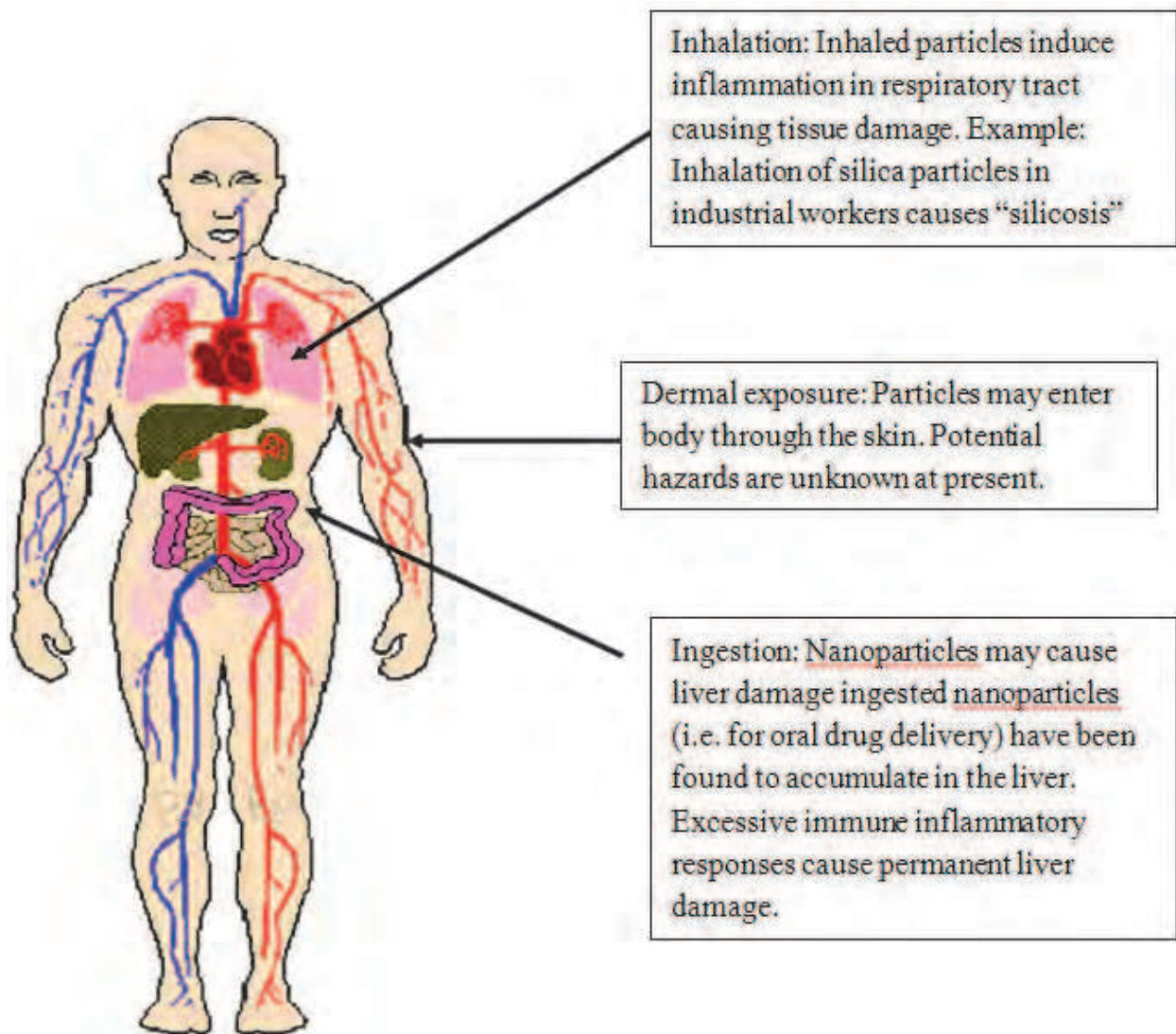


Fig. 2. Entrances of nanoscale materials into the body through inhalation, dermal exposure, and ingestion, resulting in many potential hazards [25].

Lung disease involves many illnesses, such as bronchitis, asthma, chronic obstructive pulmonary disease, influenza, pneumonia, tuberculosis, cancer, and many other breathing-related illnesses [5]. Recent studies have shown that some lung diseases, such as bronchitis and asthma, are directly linked to the uptake of nanomaterials. After the inhalation of nanomaterials, they can be deposited throughout the entire respiratory system, beginning in the nose to the inside of the lung, which has airways that transport air combined with nanomaterials in (mostly) and out (rarely) of the body. Because of the larger surface area of lungs, nanoparticles have a primary entry route. Although larger particles (more than $10\ \mu\text{m}$) tend to be deposited in the upper part of the respiratory system and removed easily by the body through coughing and sneezing, smaller nanoscale particles can reach the gas exchange surfaces and remain there for a longer period of time. This is where the real problem begins [8].

Broken surfaces and other damage in the lung and other parts of the respiratory system accelerate the penetration of nanomaterials into the surrounding tissue, resulting in faster-growing lung diseases [4]. Also, when nanoparticles enter the blood stream, they can be

Type of Material	Particle Size (nm)	Surface Area (m ² /g)	Charge/Zeta Potential (mV)	Biological Toxicity
Alumina	116	13.37	45-50 (pH 5.5-6.5)	Protein (BSA) adsorption with time IEP shifts with pH and surface area
PEG Quantum Dots	10	—	—	Retention of Q dots in liver, spleen, and bone marrow
MWCNT	10-20	40-300	—	Cytotoxicity: alveolar macrophages at high dose
SWCNT	1.4	270	—	Cytotoxicity: alveolar macrophages at low dose; transient inflammatory and cell injury
Titania	300nm(rutile)	6	—	Short-term reversible inflammation
	Rods(20-233)	26.5	—	Short-term reversible inflammation
	(anatase rods)	—	—	Minor adverse lung tissue reaction
	Spherical(5-6) (anatase spherical powder)	169.4	—	Short-term reversible inflammation Minor adverse lung tissue reaction
Quartz	1.5μm	4	—	High pulmonary toxicity
PTFE	20	—	—	Cell death-15 min. exposure
	130	—	—	No ill effects
Emulsifying Wax	74.7 ± 53.4 (neutral)	—	-14.1 ± 2.1	No BBB; permeation ability in low conc.
	127.1 ± 70.6 (anionic)	—	-59 ± 2.9	No BBB; permeation ability in low concentrations
	97.2 ± 68.9 (cataionic)	—	45.2 ± 3.5	Toxic at brain microvasculature endothelium
Ceria	3-5	—	—	Radio protection, nontoxic at low/medium dose
Yttria	50	—	—	Neuroprotection against oxidative stress

Table 1. Relationship between nanoparticle size and nanoparticle toxicity [8].

delivered to organs and tissues in the entire body, including the brain, heart, liver, kidneys, spleen, bone marrow, and nervous system [40]. Unlike larger particles, nanoparticles can reach the cell mitochondria and cell nuclei of these organs, which in turn cause DNA mutation and induce major structural damage and cell death [25,28,41]. In this case, particle size and shape are the major factors in determining particle toxicity.

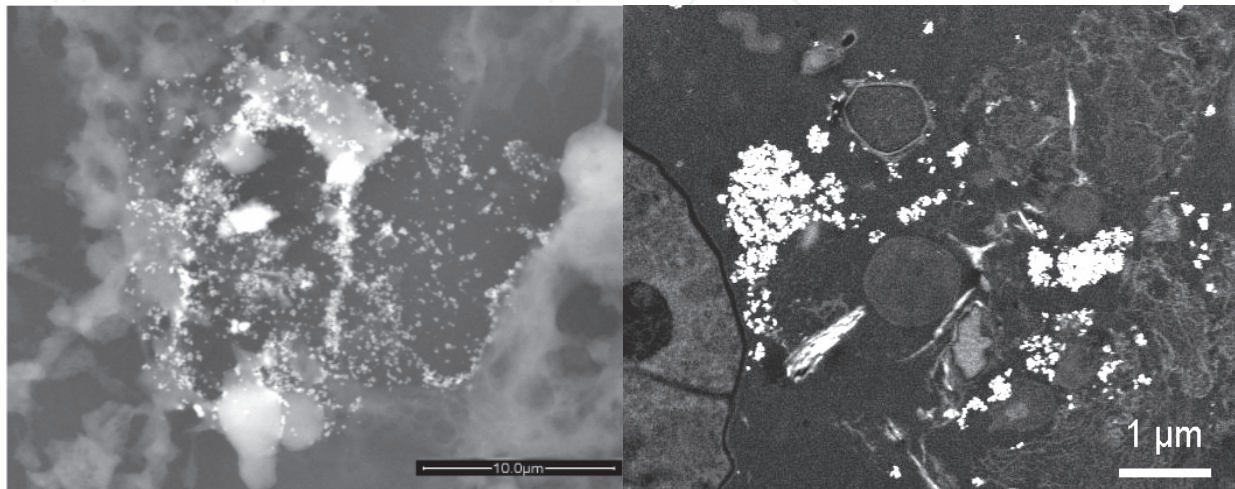


Fig. 3. Nanoparticles of lead compound located in lung where patient was affected by multiorgan granulomatosis (left), and scanning transmission electrograph of ceria nanoparticles exposed to clearing sludge (high-density cerium oxide nanoparticles are bright) (right) [29,45].

One latest study showed that, after 12 weeks of inhalation tests, small TiO_2 nanoparticles 20 nm in size were characterized by a longer retention time in the lungs of rats and increased translocation to interstitial sites than larger TiO_2 nanoparticles 250 nm in size [4,50-52]. Another study in healthy animals also showed that inhalation of metallic nanoparticles (less than 30 nm) into the circulatory system was much faster than that of non-metallic nanoparticles (between 4 nm and 200 nm) [53]. Although the mechanism of nanomaterial penetration is not fully understood, it is believed that nanoparticles can be absorbed by lung cells and induce local effects, leading to long-term consequences of airway inflammation, bronchitis, asthma, emphysema, lung cancer, neurodegenerative diseases, and cardiovascular effects [4-6].

Carbon-based nanomaterials (CBNs) in different forms of fullerenes, single- and multi-walled carbon nanotubes (SWCNTs and MWCNTs), and carbon nanoparticles and nanofibers are being used in a number of different applications [1-3]. The shape of CBNs is an important factor in determining its toxicity [42]. Some CBNs are structurally similar to asbestos, raising concerns that widespread use of carbon nanotubes may lead to mesothelioma, cancer of the lining of the lungs caused by an exposure to asbestos. In particular, the needle-like fiber shapes of CNTs are more toxic than other CBNs are to human skin fibroblasts [46-49]. MWCNTs and SWCNTs have strong chemical stability, and when inhaled, they cannot be easily dissolved in the body, which in turn could damage cells, DNA, and surrounding tissues [42-44]. Generally, SWCNTs are more toxic than MWCNTs because of their size [6]. Recent studies have also shown that sidewall-functionalized MWCNTs and SWCNTs were less toxic to human cells than those without

functionalization. Also, it is interesting to note that CNTs synthesized by a catalytic chemical vapor deposition are not toxic to human umbilical vein endothelial cells [4,32-34]. Although nanomaterials have superior properties in various applications, they can be very dangerous if not properly handled. Toxicity of nanomaterials has not been completely identified yet, and most studies have mainly focused on acute and liver toxicity [4,49]. Long-term toxicity of nanomaterials and examination of chronic exposure must be studied in detail to understand the mechanisms involved. Even though several factors are involved in nanomaterial toxicity, more efforts and time are needed to conduct research on nanoscale products and lung and other diseases [6,50].

4. Protection methods

Hazard reduction of nanomaterials is necessary for students, engineers, and health professionals working on their production, processing, and analysis, as well as workers and consumers in contact with commercial products [5,35,36]. Table 2 provides a hierarchy of the exposure controls of nanomaterials at different categories, such as elimination, substitution, engineering, administration, and personal protective equipment [9,37].

Control Methods	Process, Equipment, and Tasks
Elimination	Change design to eliminate or minimize hazardous materials.
Substitution	Replace high-hazard material with a low one (e.g., environmental).
Engineering	Use isolation/enclosure, ventilation, filtration, and collection.
Administration	Adhere to procedures, policies, shift design, and new rules and regulations.
Personal Protective Equipment	Use respirators, clothing, gloves, goggles, and ear plugs.

Table 2. The hierarchy of exposure controls of nanomaterials and their controls [9,37].

The processing, equipment, and job tasks associated with the control methods are as follows: *i*) change the design to eliminate or minimize hazardous materials; *ii*) replace a high-hazard material with a low one; *iii*) use isolation, ventilation, filtration, and dust collection; *iv*) adhere to procedures, policies, shift design, and new rules and regulations; and *v*) use respirators, clothing, gloves, goggles, and ear plugs. Figure 4 shows some methods of protection that should be used during the production and use of nanomaterials [5,35], which are outlined as follows [4-6]:

- Students, workers, engineers, doctors, and scientist who are working with nanomaterials and devices are recommended to wear a disposable, typically plastic, body covering over their work clothes during high-exposure activities and to wear long gloves pulled over their sleeves to minimize wrist exposure and other contamination. Other recommendations are antistatic shoes to prevent ignition by static charges, and sticky mats at laboratory entrances to prevent the accidental transfer of nanomaterials in and out of the working area [5].

- The hazardous effects of nanomaterials need to be reduced during their production and processing. The waste of nanomaterials should be limited. Outputs are sometimes more hazardous than the products or wastes from such activities [5].
- Workers who inhale nanomaterials are advised to consume milk and unrefined sugar to reduce the toxicity level of nanomaterials [5].
- Nitrile gloves or wrist-length disposable nitrile gloves with extended sleeves must be worn during the handling of nanomaterials (Figure 4). These gloves need to be changed frequently [5].
- For eye protection, safety glasses with side shields must be on the face during the use of nanomaterials in the form of solids, liquids, and aerosols [5].
- Volumes of liquid-based nanomaterials must be limited to the milliliter range (< 200 ml) in a sealed container when not in use [5].
- Total particle masses must be limited to the milligram range (< 200 mg) and must be manipulated within a high efficient particulate air (HEPA)-filtered laboratory exhaust hood over water-soaked absorbent paper to capture any spilled materials [5].
- Containers of nanomaterials must be labeled with a sign indicating “NANOMATERIALS” [5].
- Nanomaterials are considered to be hazardous materials, so workers should follow all the safety rules necessary in the field and laboratory [5].
- The use of nanomaterials increasing worldwide brings with it several concerns for worker and user safety. Thus, new measurement devices should be developed and used in the specified areas where nanomaterials and devices are produced and utilized.

In addition to the previous information, the National Institute for Occupational Safety and Health (NIOSH) has provided sequential steps for students, workers, engineers, and others who are involved in nanotechnology-related teaching, research, and development [5,38]. These steps, shown in Figure 5, will potentially reduce the risk of exposing nanomaterials to personnel and consumers [5,38].



Fig. 4. Simple protection methods for using potentially hazardous engineered nanomaterials in laboratory conditions.

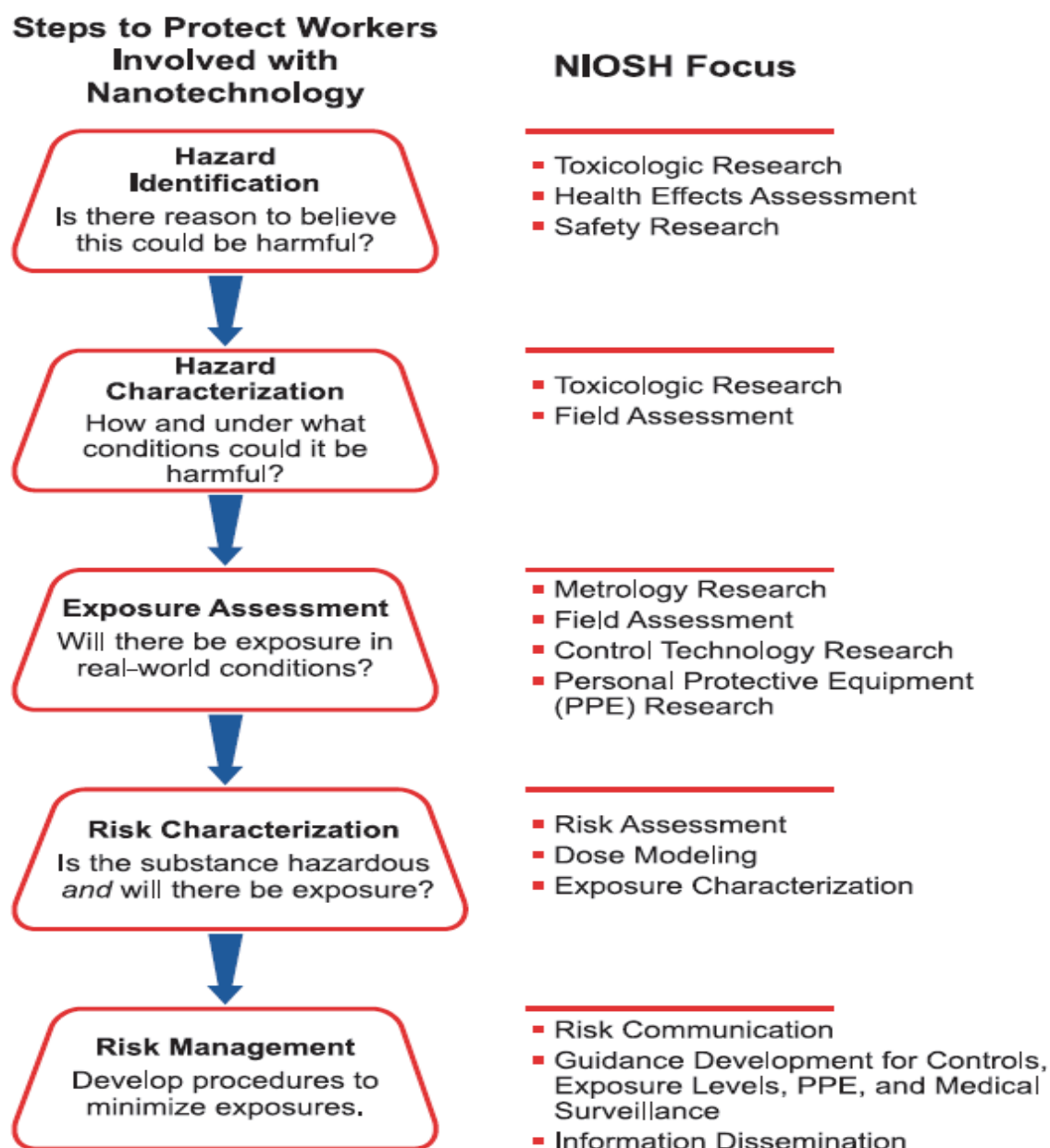


Fig. 5. Steps of NIOSH for workers/students involved in nanotechnology processes [5].

5. Conclusions

Although nanomaterials have superior properties for various applications, these materials could be more hazardous to human than their microscale equivalent if not properly handled or used. The nanomaterials mainly exposed through inhalation of suspended nanoscale particulates result in the inflammation of airways, bronchitis, asthma, emphysema, lung cancer, neurodegenerative diseases, and cardiovascular effects. Toxicity of nanomaterials has not been completely identified yet, and most studies have focused primarily on acute liver toxicity. The long-term toxicity of nanomaterials and examination of chronic exposure to these materials must be studied in detail to understand their toxicology mechanisms in the lungs and other organs. Even though several factors are involved in the toxicity of nanomaterials, more efforts and time are needed to study nanoproducts, their properties,

and processing. Thus, students, scientists, engineers, doctors, policymakers, and regulators working in the field should take all the necessary precautions to protect themselves during the production, handling, and consumption of nanomaterials.

6. Acknowledgment

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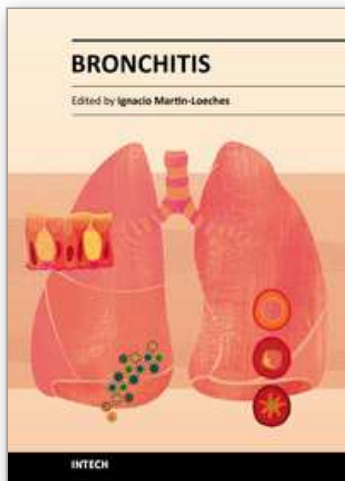
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Lung parenchyma has been extensively investigated. Nevertheless, the study of bronchial small airways is much less common. In addition, bronchitis represents, in some occasions, an intermediate process that easily explains the damage in the lung parenchyma. The main target of this book is to provide a bronchial small airways original research from different experts in the field.

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