NANOTOXICOLOGY: TOXICOLOGICAL AND BIOLOGICAL ACTIVITIES OF NANOMATERIALS

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Summary

All aspects of our life will benefit from the revolution in nanotechnology. This revolution will necessitate large scale production of nanosize particles/structures, new formulations and novel surface properties to meet demands of novel functions. Meanwhile, the rapidly development of nanotechnology is likely to become new sources of human or environmental hazards through inhalation, ingestion, skin uptake, or injection of engineered nanomaterials in workplace or the use of consumer products. So far, research results suggest that nanoparticles may cause adverse effects on human health at their portal of entry, which show difference from the bulk materials of the same chemical composition. Taking the lung as an example, some nanoparticles can escape the normal defenses and translocate from their portal of entry to induce diverse impacts in other organs, and in some cases, the nanoparticles stay in the organ for a long time and be not easily excreted from the body. On interaction at a cellular level, some nanoparticles easily enter into the cells, etc. In order to gain a sustainable development, new technology always needs a good balance between the benefit and risk.

Nanotoxicology is intended to address the toxicological activities of nanoparticles and their products to determine whether and to what extent they may pose a threat to the environment and to human health, and defined as the study of the nature and mechanism of toxic effects of nanoscale materials/particles on living organisms and other biological systems. It also deals with the quantitative assessment of the severity and frequency of nanotoxic effects in relation to the exposure of the organisms. The knowledge from nanotoxicological study will be the base for designing safe nanomaterials and nanoproducts, and also direct uses in the nanomedical sciences. This chapter consists of five sections with a brief introduction, the target organ toxicity of nanoparticles in different biological systems, the ADME (absorption, distribution, metabolism and excretion) of nanoparticles in vivo following different exposure routes, the cytotoxicity and molecular nanotoxicology of nanoparticles.

1. Introduction

With the fast development of nanotechnology, industries are currently involved in nanotechnology-related activities, among which the manufactured nanoscale materials or engineering nanoparticles are using in a wide range of products. It is known that nanostructured materials or nanoscale particles possess many novel properties such as self-assembly, size effects, large surface area, ultrahigh reactivity and quantum effects because of their very small size and unique structures. According to data collected by the National Nanotechnology Initiative (NNI), the quantity of manufactured nanoscale material is growing significantly every year. Business Communications Company has projected a $10 billion global demand for nanoscale materials, tools, and devices in 2010 (see website: http://www.nano.gov/). This large increase in demand and production could lead to enormous exposures of humans and other organisms to nanomaterials/nanoparticles. What happens with these very small-size materials when
they entered our body, in particular what can be expected with the increased surface reactivity which may lead to completely different biological effects in vivo as compared to the bulk material of the identical chemical composition and the same quantity. Of cause they can either be positive and desirable, or negative and undesirable, or a mix of both, these mostly depend on how to utilize them.

Nanotoxicology is defined as the study of the nature and mechanism of toxic effects of nanoscale materials/particles on living organisms and other biological systems. It also deals with the quantitative assessment of the severity and frequency of nanotoxic effects in relation to the exposure of the organisms. In fact, scientists have studied the healthy effects of exposure to airborne nanoparticles for years and have shown some unexpectedly adverse health effects of nanosized particles in vivo. For instance, the epidemiological investigations have found the associations of incidence of a disease and mortality with the concentrations and the sizes of the airborne particles in the environment. The increase of mortality might result from the abundant increase of nanoparticles. Recently, the biological/toxicological effects of manufactured nanomaterials and nanoparticles have attracted much attention and been seriously discussed (Service, 2003; Kelly, 2004; Brumfiel, 2003; Zhao et al., 2008).

From the fact that the sizes of the nanoparticle and the biological molecule are comparable (Figure1), one easily bethinks of such a consequence that the nanoparticle may easily invade the natural defense system of human body or other species and easily enter the cells to affect cellular functions. The existing knowledge reminds that when molecules are small enough, it is possible for them to slip past the guardians in our respiratory systems, skip through our skin into unsuspecting cells, and (sometimes) cross through the blood-brain barrier (BBB). More essentially, the life process is mainly held out by a series of biochemical reactions in vivo. Manufactured nanoparticles possess ultra huge surface area, ultrahigh reactivity, highly efficient catalysis, and nanostructures, etc., do they interfere the normal biochemical reactions in vivo when entering the human body? Are these interferences beneficial or harmful to the life process? How to avoid the harmful effects, and how to utilize the beneficial effects? For instance, one sees the similarity in geometric structures of manufactured nanocage (fullerene) and the biological protein (clathrin) in Figure 1, they all consist of the pentagon and hexagon rings.

In fact, many knowledge gaps need to be filled in. For instance, the large alteration in physicochemical properties of nanomaterials as compared to the bulk material of the same chemical form, and the large alteration in physicochemical characteristics between different sizes of the same nanomaterials will undoubtedly lead to different biological effects in vivo. So the existing database of safety evaluation for the bulk materials, including the effects on health and the environment is probably no longer valid when extrapolating and applying them for the safety assessment of nanomaterials.
In any application or even at the initial stages of the research and development, these nanoparticles easily enter the environment via various routes, and ultimately enter human body through direct routes such as dermal and oral exposures, nanodrugs, or through indirect routes such as the food chain, etc. For nanoparticles, except the very strong size-effects, other unique properties such as the tremendous surface, anomalous interface, complicated reactivity, quantum effects, etc. can also lead to changes in physicochemical properties which naturally alter the biological activities in vivo. These have been demonstrated by the reported data and will be summarized and discussed in the following sections of this chapter (Warheit et al., 2004; Lam, 2004; Chen, 2007; Feng et al., 2009; Fischer et al., 2007; Wang et al., 2005; Zhao et al., 2007; Nel et al., 2009). Thus, in this chapter, the toxicological effects of nanomaterials will be clarified in detail at whole-animal, cellular and molecular levels based on the experimental findings from both the in vivo to in vitro models.

2. Target Organ Toxicity of Nanoparticles

As different tissues and organs have different compositions, structures and functions, toxic responses are mostly different once nanoparticles (NPs) enter different organs. Human skin, intestinal tract and respiratory tract are always in direct contact with the environmental nanoparticles. For instance, skin, as a structural barrier between the environment and the body, plays an important role to protect against break-in of exogenic particles. Respiratory tract, generally divided into three segments,
respiratory tract, respiratory airways and lung, most of which exists merely as a piping system for air to travel in the lungs. Gastrointestinal tract, also known as the digestive tract, can uptake, transport, digest and adsorb various substances such as nutrients, water and vitamins from food. On the other hand, the gastrointestinal tract is also designed as a barrier to restrain the entry of pathogens, toxins and undigested macromolecules. As such, these potential exposure routes are likely to be the first portal of entry for nanoparticles invading into the human body. In addition, other physiological systems such as cardiovascular system and central nervous system may have chances to interact with exogenous nanoparticles circulated or transported from the above exposure routes. So, they may also be a specific target for any type of nanoparticle into the human body.

2.1. Respiratory System

We may say that we inaugurate our life with an inspiration of air. However, the air we breathe is not so pure as we would desire it to be, usually containing other pollutants such as by-products of the combustion processes related to fires, heating, industrial and automotive processes. So, the toxicity research on NPs in vivo has been carried out on respiratory system of mammalian.

2.1.1. Deposition of Nanoparticles in the Respiratory Tract

Respiratory system can be further divided into different target zones such as nasopharyngeal, tracheobronchial and alveolar regions. Specific defense mechanisms may protect the mammalian organism from harmful materials at the portal of entry, however, these defenses may not always be as effective for NPs. When the NPs are inhaled, their deposition, clearance, and translocation within the respiratory tract will be different from the larger particles.
According to the diffusion motion, exposure to airborne NPs via the inhalation route will deposit throughout the entire respiratory tract, starting from nasopharyngeal and tracheobronchial, down to the alveolar regions. Depending on the particle size, the deposition fractions of inhaled NPs in these regions show significant difference. For instance, 90% of inhaled 1 nm particles are deposited in the nasopharyngeal compartment, only ~10% in the tracheobronchial region, and essentially none in the alveolar region. On the other hand, 5 nm particles show about equal deposition of ~30% of the inhaled particles in all three regions; 20 nm particles have the highest deposition efficiency in the alveolar region (~50%), whereas in tracheobronchial and nasopharyngeal regions this particle size deposits with ~15% efficiency (Figure 2) (ICRP, 1994). These different deposition efficiencies should have consequences for potential effects induced by inhaled NPs as well as for their translocation beyond the respiratory tract.

2.1.2. Clearance of Nanoparticles in the Respiratory Tract

Pulmonary retention and clearance of microsized particles have been studied for many
years. While, the recent studies on occupational and environmental exposure of nanoparticles (NPs) generated a considerable amount of new knowledge regarding the clearance of NPs in the respiratory tract. The clearance of deposited particles in the respiratory tract is mainly by physical translocation to other sites or chemical clearance. Chemical dissolution in the upper or lower respiratory tract occurs for biosoluble NPs in the intra-cellular or extra-cellular fluids. The solutes and soluble components can then undergo absorption and diffusion in other subcellular structures or binding to proteins in cells and may be eventually cleared into blood and lymphatic circulation. This clearance mechanism can happen at any location within the three regions of the respiratory tract, depending on the pH of local extracellular and intracellular compartments.

The clearance for insoluble or poorly soluble NPs in the respiratory tract is basically via physical translocation. The efficiency of this clearance depends highly on the site of deposition and particle size. The NPs trapped within the mucociliary escalator from the upper airways (nasopharyngeal and tracheobronchial) is expelled by pushing the mucus toward the mouth, hence, it is a relatively rapid process (Kreyling and Scheuch, 2000). For NPs within the alveolar regions, the most prevalent clearance is mediated by macrophage phagocytosis, which highly depends on the efficiency of alveolar macrophages to “sense” deposited particles, move to the site of their deposition, phagocyte them, and then move towards the mucociliary escalator (Kreyling and Scheuch, 2000).

2.1.3. Nanotoxic Response of Respiratory System

The epidemiological studies have found a correlation between exposure to respirable airborne particulate matter (PM) and increased mortality and adverse respiratory health effects, including the development of emphysema, chronic bronchitis, and asthma (Samet, 2000; Hoet, 2004). As the most toxic component of airborne particulate matter, nanoparticles have uncontrolled access to the cells of the airway and even intracellular components because of their size. Hence, deposition of NPs in the alveolar spaces of the lung plays a central role to pulmonary toxicity. When inhaled, NPs deposit dispersedly upon the alveolar surface, which likely leads to a scattered chemoattractant signal, resulting in lower recognition and alveolar macrophage responses (Kreyling et al., 2006). The biopersistence of inhaled particles is an important characteristic dictating the level of inflammation and tissue injury.

The representative studies of pulmonary inflammation and fibrosis induced by nanoparticles in experimental animal was first reported by Lam and Warheit who demonstrated that intratracheal instillation of single-walled carbon nanotube (SWNTs) and multi-walled carbon nanotube (MWNTs) under a certain dose induced a pulmonary granuloma formation and some interstitial inflammation (Figure3) (Lam, 2004; Warheit, 2004). Further study indicates both SWNTs and MWNTs could induce the alteration of cell structures (Jia et al., 2005). For instance, when exposed to 5 μg/mL SWNTs, the macrophage cell exhibited condensed folds, while the nucleus degenerated and the nuclear matrix reduced when treated with MWNTs (Figure4). At a higher dose level of 20 μg/mL, cells exposed to SWNTs became swelled and vacuolar, and presented phagosomes explicitly; while in those exposed to MWNTs, the chromatin was concentrated, selenodont border and vacuole in cytosol were presented. All the above
alterations show signs of cell apoptosis. It is important to note that the cell apoptosis induced by SWNTs and MWNTs under a certain dose is much different from the cell necrosis, which was accompanied with inflammation. Recent studies on intratracheal instillation of nanoparticles in rats showed intratracheally instilled ferric oxide nanoparticles (20 nm) induced some clinical pathological changes such as follicular hyperplasia, protein effusion, pulmonary capillary vessel hyperaemia and alveolar lipoproteinosis in lung (Figure 5). The sustain burden of particles in alveolar macrophages and epithelium cells has caused lung emphysema and pro-sign of lung fibrosis (Zhu et al., 2008). Most recently, an age-related difference in the pulmonary response to the inhaled SiO₂ nanoparticles has been found, i.e. the same respiratory exposure caused much severer pulmonary inflammation in old rats than in young or adult rats.

Figure 3. Lung tissue from mice instilled with 0.5 mg of a test material per mouse and killed 7 d after the single treatment. (a) Serum control; (b) carbon black (CarboLex nanotubes); (c) silica quartz; (d) CNT; (e) RNT (raw nanotube); (f) PNT (purified nanotube).
Figure 4. Ultrastructural changes of phagocytes induced by SWNTs and MWNTs (with diameter of 10-20 nm) particles at different doses (Jia et al., 2005). (a) Control; (b) control; (c) 5 μg/mL SWNTs; (d) 20 μg/mL SWNTs; (e) 5 μg/mL MWNTs; (f) 20 μg/mL MWNTs.
Figure 5. Histopathology of lung at days 7 and 30 after intratracheal instillation of particles or saline (hematoxylin–eosin stain, magnification = 50). Follicular hyperplasia of the lymph node was formed at trachea forks (dark arrow). (A) Control group; (B) days 7 after instillation of 0.8 mg/kg bw 22 nm-Fe$_2$O$_3$; (C) days 30 after instillation of 0.8 mg/kg bw 22 nm-Fe$_2$O$_3$; (D) days 7 after instillation of 0.8 mg/kg bw 280 nm-Fe$_2$O$_3$; (E) days 30 after instillation of 0.8 mg/kg bw 280 nm-Fe$_2$O$_3$; (F) days 7 after instillation of 20 mg/kg bw 22 nm-Fe$_2$O$_3$; (G) days 30 after instillation of 20 mg/kg bw 22 nm-Fe$_2$O$_3$; (H) days 7 after instillation of 20 mg/kg bw 280 nm-Fe$_2$O$_3$; (I) days 30 after instillation of 20 mg/kg bw 280 nm-Fe$_2$O$_3$. (Zhu et al., 2008)
2.2. Gastrointestinal System

The gastrointestinal tract is one of the largest immunological organs of the body, containing more lymphocytes and plasma cells than the spleen, bone marrow and lymph nodes. It is considered that the exogenous sources of ingestion exposure primarily results from hand-to-mouth contact in the workplace. Alternatively, NPs can be ingested directly via food, water, drinking, drugs or drug delivery systems. In addition, NPs cleared from the respiratory tract via the mucociliary escalator can subsequently be ingested into the gastrointestinal (GI) tract. Thus, gastrointestinal tract is considered as an important target for NPs exposure.

Figure 6. The microscopic pictures (×100) show the pathological changes in kidney tissues of experimental mice of the control (a); 500 mg/kg nano-copper exposed group (b); 1851 mg/kg nano-copper exposed group (c) 5000 mg/kg nano-copper exposed group (d). A: renal glomerulus and B: Bowman’s capsule.

So far, our research group has investigated the acute oral toxicity of several types of nanoparticles with gastrointestinal tract exposure. For instance, we compared the oral toxicity of copper nanoparticles (23.5 nm) and micro particles (17 μm) in mice (Chen et al. 2006). In 17 μm particles treated mice only few mice exhibited symptoms of poising, however, all by nano-copper treated mice appeared obviously symptoms of alimentary canal function disorder, such as loss of appetite, diarrhea and vomiting, etc. Further pathological examination revealed grave injuries on kidney, liver and spleen in mice exposed to nano-copper particles, but not found in mice exposed to micro-copper...
particles on mass basis (Figure 6–Figure 8). When mice were orally administrated with 20 nm and 120 nm ZnO NPs at different doses, we found that the liver, spleen, heart, pancreas and bone became the target organs whose damages show different dose-response relationship (Wang et al., 2008). The 120 nm ZnO treated mice had a positive dose-effect pathological damage in stomach (inflammation in gastric lamina propria, submucosa or serosa layer), liver (fatty degeneration of hepatocytes around central vein or portal area), heart (fatty degeneration of cardiovascular cells) and spleen (largement of splenic corpuscle), whereas, 20 nm ZnO displayed a negative dose-effect damage in the above mentioned organs.

Figure 7. The microscopic pictures (×200) show the pathological changes in liver tissues of experimental mice of the control (a); 500 mg/kg nano-copper exposed group (b); 1851 mg/kg nano-copper exposed group (c) and 5000 mg/kg nano-copper exposed group (d). A: steatosis.
Figure 8. The microscopic pictures (×40) show the pathological changes in spleen tissues of experimental mice of the control (a); 500 mg/kg nano-copper exposed group (b); 1851 mg/kg nano-copper exposed group (c) and 5000 mg/kg nano-copper exposed group (d). A: splenic unit and B: lymphocytes.

2.3. Cardiovascular System

The cardiovascular system is composed of the heart, blood vessels, vasculature, the cells and plasma that make up the blood. The principal function of the heart is to continuously pump blood around the cardiovascular system. It receives both sympathetic and parasympathetic nerve fibres which alter the rate of the beat, but they do not initiate the contraction. The blood vessels of the body represent a closed delivery system, which functions to transport blood around the body, circulating substances such as oxygen, carbon dioxide, nutrients, hormones and waste products.

The epidemiologic investigations have shown a direct credible relationship between ambient air particulate pollution and a consistent association with increased health effects specifically leading to cardiovascular diseases. The concentration response relationship between PM2.5 and daily deaths was reported to cause 100,000 deaths annually in the United States (Schwartz et al., 2002). In a recent comprehensive review of epidemiologic studies it was shown clearly the pathophysiological changes of cardiovascular diseases had close association with exposure to ultrafine particles (UFPs) in air.

In the case of manufactured nanoparticles, a single intrapharyngeal instillation of single-
wall carbon nanotubes (SWCNTs) can induce activation of heme oxygenase-1 (HO-1), a marker of oxidative insults, in lung, aorta, and heart tissue in HO-1 reporter transgenic mice (Li et al. 2007). Furthermore, the C57BL/6 mice exposed to SWCNT (dose: 10 and 40 μg/mouse) developed some pathophysiological changes related to cardiovascular diseases such as mitochondria DNA damage, elevation of mitochondrial glutathione and protein carbonyl levels (Li et al., 2007). In order to study the age-related difference in cardiovascular responses to SiO2 nanoparticles inhalation exposure, we designed a novel nanoparticles exposure system, a sealed Plexiglas exposure chamber specifically mimicking natural (physiologic) inhalation, and investigated the toxicity sensitivity of nanoparticles in different ages (young, adult, old) of rats (Chen et al., 2008). We measured and analyzed the changes in serum biomarkers, hemorheologic, heart injury, and pathology in rats of different ages, and found that the SiO2 nanoparticles inhalation under identical conditions caused severe myocardial ischemia, significant elevation of blood viscosity and fibrinogen concentration in old rats, yet less change in young and adult rats. The results indicate that old individuals are more sensitive to nanoparticle exposure than the young and adult rats (Chen et al., 2008) (Figure 9).

From above findings about cardiovascular response to nanoparticles exposure, one may raise a new and significant question: whether the health effects of air particulate is dominated by the nanosized fraction in air. Moreover, besides the factor of size, other physicochemical parameters of nanoparticles, such as shape, crystal structure, solubility, surface area, surface charge, surface coating may also play key roles on the cardiovascular events,

**Figure 9.** With identical inhalation of nanoparticles, myocardial ischemic damage was seen only in older rats.
Figure 10. Changes in whole blood viscosity ($\eta_b$) in different-aged rats who inhaled air containing manufactured SiO$_2$ nanoparticles. $\eta_b$ (mean (SD)) is plotted against shear rate at intervals from 1 S$^{-1}$ to 200 S$^{-1}$ and hematocrit at 41%. $\eta_b$ was significantly elevated in the exposed group of old rats (a), but no statistical differences were observed between the exposed and control groups in each of the young (b) and adult (c) groups. Two asterisks (**) represents $p < 0.01$ in the one-way ANOVA $t$-test. Panels d and e show the changes in fibrinogen and plasma viscosity ($\eta_p$) as a function of age. $p$, A, and B are defined in Figure 2. A and B are the Duncan class of Duncan’s multiple-range test. (Chen et al., 2008)

2.4. Central Nervous System

The central nervous system (CNS), consisting of the brain and spinal cord, is responsible for receiving and interpreting signals from the peripheral nervous system and also sends out signals to it, either consciously or unconsciously. Although respiratory system is considered to be the main portal of entry for inhaled nanoparticles, extrapulmonary translocation after respiratory tract deposition is likely to happen via accidental or occupational acute exposure (Nemmar et al., 2002). It is also possible that...
inhaled UFPs, by virtue of their extremely small size may deposit in the olfactory mucosa and then translocate in the central nervous system, which in turn might cause neurotoxicity. Recent studies support the concept that the CNS may be an important target organ for nanoparticle inhalation or intranasal instillation exposure (Oberdörster et al., 2004; Elder et al., 2006).

The inhaled ultrafine carbon (35 nm) and manganese oxide nanoparticles (30 nm) can translocate in the brain via the olfactory neuronal pathway (Oberdörster et al., 2004; Elder et al., 2006). In particular, some investigations have indicated that inhaled or intranasally instilled ultrafine particle may trigger a proinflammatory response in nervous tissue. For instance, intranasally instilled ultrafine carbon black (14 nm) can induce inflammatory changes (interleukin-1β, tumor necrosis factor-α and chemokines mRNA) in the brain olfactory bulb (Tin-Tin-Win-Shwe et al., 2006). Further, the size-dependent potential damage of nanoparticles on CNS was also demonstrated by the study of intranasal instillation of carbon black (CB) nanoparticles in mice. The proinflammatory responses were observed in brain olfactory bulb of the 14nm CB treated mice but not in the 95nm CB treated ones. The intranasal instillation of ufCB may influence the brain immune function depending on their size. (Tin-Tin-Win-Shwe et al., 2006). In our recent study, we found a time-dependent translocation pattern and potential damages of TiO$_2$ nanoparticles on CNS through intranasal instillation. We collected the brain tissues and measured the accumulation and distribution of TiO$_2$ (Figure11). The tissues were analyzed with histopathology, oxidative stress, and inflammatory markers at post-instillation time points of 2, 10, 20 and 30 days. Results indicated that the instilled TiO$_2$ directly entered the brain through olfactory bulb in the whole exposure period, especially deposited in the hippocampus region and induced pathological changes in the olfactory bulb and hippocampus regions (Wang et al., 2008).

Figure 11. SRXRF mapping of Ti-element distribution in the brain sections at 30 days after intranasal instillation of the different-sized TiO$_2$ particles. In the control mice, the Ti contents are lower than the detection limit of SRXRF and the mapping is not available.
2.5. Skin

The human skin, the largest organ in the body, is composed of three layers - epidermis, dermis and subcutaneous, protecting against the environment with a surface area of nearly 18,000 cm\(^2\). The outer portion of the epidermis, called stratum corneum is a 10 \(\mu\)m thick keratinized layer of dead cells and is difficult to pass through by ionic compounds or water soluble molecules. The surface of epidermis is highly microstructured, having a scaly appearance as well as pores for sweat, sebaceous glands, and hair follicle sites. Skin is considered to be the barrier between the well-regulated “milieu interieur” and the outside environment. It also has a relative large surface area for exposure, serving as one of the principal portals of entry by which nanomaterials can enter the body.

Currently, there is a lack of information on whether nanoparticles can be absorbed across the skin’s stratum corneum barrier or whether systemically administered particles can accumulate in dermal tissue. The tendency for nanomaterials to traverse the skin is a primary determinant of its dermatotoxic potential. That is, the nanomaterials or nanoparticles must penetrate the uppermost stratum corneum layer in order to gain entrance to the viable epidermis and exert toxicity in the lower cell layers. Up to now, nanoparticle dermal penetration is still under controversial. A current area under discussion is whether or not TiO\(_2\) NPs in commercially available sunscreens can penetrate the skin to enter the body. Several studies in murine, porcine, or human skin have confirmed that TiO\(_2\) NPs remained on the skin surface or the outer layers of the skin and had not penetrated into or through the living skin (Lademann et al., 1999; Pflücker et al., 2001; Schulz et al., 2002). However, there is some evidence which suggests the NPs may penetrate into the epidermis or dermis. Bennat and Müller-Goymann (2000) applied TiO\(_2\) NPs to human skin either as an aqueous suspension or oil-in-water emulsion and evaluated skin penetration using the tape stripping method (Bennat and Müller-Goymann, 2000). They observed that TiO\(_2\) NPs apparently penetrated deeper into human skin when applied as an oil-in-water emulsion, and that penetration was greater when applied to hairy skin, which suggest that TiO\(_2\) NPs penetrate surface through hair follicles or pores.

Nanoparticles caused dermatotoxicity was reported by both \textit{in vivo} or \textit{in vitro} experiments. In an animal model study, both 0.5- and 1.0-\(\mu\)m beryllium particles could penetrate the stratum corneum and develop hapten-specific, cell-mediated immune responses (Tinkle et al. 2003). In an \textit{in vitro} study, Shevedova \textit{et al.} (2003a) reported that SWCNT caused a significant dose-response reduction of cell viability and oxidative stress biomarkers (e.g., antioxidant reserve), and a significant increase in lipid peroxides in human epidermal keratinocytes (0, 0.06, 0.12 and 0.24 mg/mL of SWCNT for 18 hours), suggesting an increase of cutaneous toxicity.

In the recent years, a majority of nanotoxicity research is focusing on \textit{in vitro} systems. However, the data from \textit{in vitro} studies easily mislead the safety assessment efforts. The data will require verification from \textit{in vivo} animal experiments. On the other hand, \textit{in vivo} systems are extremely complicated and the interactions of the nanostructures with biological components, such as proteins and cells, could lead to unique biodistribution, clearance, immune response, and metabolism. Thus, an understanding of the
relationship between the physical and chemical properties of the nanostructure and their in vivo behavior would provide a basis for assessing nanotoxicity and more importantly may lead to predictive models for nanotoxicity assessment.

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Oberdörster G., Sharp Z., Atudorei V., Elder A., Gelein R., Kreyling W., Cox C. (2004). Translocation of inhaled ultrafine particles to the brain, Inhal Toxicol 16, 437-445. [This paper concluded from author’s studies that inhaled ultrafine carbon particles are to a significant extent translocated to the CNS.]


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paper’s investigations using optical and electron microscopy proved that neither surface characteristics, particle size nor shape of the micronized pigments result in any dermal absorption of this substance.]


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Biographical Sketches

**Professor Yuliang Zhao**’s degrees are in Chemistry (1985, Sichuan Univ.), and in Chemistry/Physics (M.D.1996 & Ph.D. 1999, Tokyo, Japan). He moved to Chinese Academy of Sciences (CAS) from RIKEN (Japan) as a Hundred Elite Professor in 2001. He is the founder of CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, and also the founder of Research Center for Cancer Nanotechnology which is a joint research center from CAS and Tianjin Cancer Hospital. His current researches mainly focus on toxicological effects of nanomaterials, biomedical functions of multifunctional nanoparticles, and nanosurface chemistry for the purposes of enhancing the biomedical functions or reducing the potential toxicity. Dr Zhao’s other research interest includes the theoretical simulation and modelling the dynamic processes of the interplay between nano-systems and bio-systems like membrane or biological channels. Prof. Zhao has published more than 120 peer-reviewed journal articles at International journals, and more than 70 research articles at domestic Chinese journals, one book “Nanotoxicology” in USA (2007), which is the first textbook in the nanotoxicology field. He is also the editor-in-chief of 10 books on biological activities and safety assessment of nanoscale materials, published by China Scientific Press (2009). He serves as editorial board member of 8 international journals, Associate Editors for Biomedical Microdevices (USA), Particle and Fiber Toxicology (UK), and Journal of Nanoscience and Nanotechnology (USA). He has been invited and given more than 110 Invited Lectures at conferences and universities/institutes worldwide.

**Professor Wei-Yue Feng** (born in 1967) obtained a B.S. in Chemistry from Fudan University in 1989, and a Ph.D. from Institute of High Energy Physics, Chinese Academy of Sciences in 1998. Since then, she has been working in the CAS Key Lab for Biomedical Effects of Nanomaterials and Nanosafety of the institute. Her current primary fields of research include nanotoxicology, proteomics and nuclear
analytical techniques application. She has published more than sixty related papers at peer-reviewed journals. Now she is a professor and a research group leader at Institute of High Energy Physics, Chinese Academy of Sciences.

Professor Bing Wang (born in 1977) obtained a B.S. in Chemistry from Shandong University in 1999, and a Ph.D. from Institute of High Energy Physics, Chinese Academy of Sciences in 2007. Since then, she has been working in the CAS Key Lab for Biomedical Effects of Nanomaterials and Nanosafety of the institute. Her primary fields of research include nanotoxicology and nuclear analytical techniques application. She has published more than ten related papers at peer-reviewed journals. Now she is an assistant professor at Institute of High Energy Physics, Chinese Academy of Sciences.

Professor Chunli Bai is Professor and Executive Vice President of the Chinese Academy of Sciences (CAS) and President of the Graduate University of CAS with more than 32,000 students, Director of Division of Chemistry and member of Executive Committee of the Presidium. He graduated from the Department of Chemistry, Peking University in 1978 and received his MS and Ph.D. degrees from CAS Institute of Chemistry in 1981 and 1985, respectively. During 1985-1987, he was at Caltech, the US for advanced study, conducting research work in the field of physical chemistry as a post-doctorate associate and visiting scholar. After his return home in 1987, he continued his research at CAS Institute of Chemistry. From 1991 to 1992, he was a visiting professor at Tohoku University in Japan. Prof. Bai has a long list of scientific publications and has won more than twenty prestigious awards and prizes for his academic achievements. Because of his meritorious service, He was elected a member of CAS and a fellow of the Academy of Sciences for the Developing World (TWAS) in 1997. He is also foreign associate of the US National Academy of Sciences, fellow of the Royal Society of Chemistry, foreign member of the Mongolian National Academy of Sciences and honorary doctor or honorary professor in several universities abroad. Prof. Bai now serves as the chief scientist for the National Steering Committee for Nanoscience. In his social activities, he is president of Chinese Chemical Society, honorary president of Chinese Society of Micro-Nano Technology (CSMNT), The Vice-President of the China Association for Science and Technology, Vice-President of TWAS, member of Bureau and Executive Committee of IUPAC. President-Elect of Federation of Asian Chemical Societies. He is the member of the International Editorial Adversary Board of JACS, Angewandte Chemie, Advanced Materials and Chemical Physics Letters.