

# Current Knowledge About Nanotechnology Safety

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Key Words: Nanotechnology, Nanoparticle, Nanomaterial, Risk, Safety, Inhalation, Ingestion, Dermal, Skin

## SUMMARY & CONCLUSIONS

This review paper provides insight into the risk faced by laboratory workers from suspected nanoparticle hazards. The potential hazard and risk is examined with respect to the dermal, inhalation, and ingestion pathways into the human body. Based on the current understanding, the risks are presented qualitatively from a system safety perspective as a function of likelihood and consequence. Without protective equipment, the likelihood of dermal exposure for carbon nanoparticles is high, but is low and very low for inhalation and ingestion pathways, respectively. The consequence for dermal exposure is likely to be dermatitis, but for the other two pathways there has been no clear evidence of any consequence. However, the consequences will be better judged after nanotechnology has had time to establish itself and more studies have been performed on the toxicological effects of nanoparticles. The surveyed papers propose that because nanoparticles vary in their chemical composition and biological and immunological properties, the risks posed by them also vary. Thus, each nanomaterial should be assessed individually for its health risks.

## 1. INTRODUCTION

Since the late 1990's nanotechnology has shot into the limelight and has been embraced by a large number of research centers, including National Aeronautics and Space Administration (NASA). Nanotechnology involves research and technology development of structures, most commonly the carbon nanotube, at the atomic, molecular or macromolecular levels, in the length scale of approximately 0.1 - 100 nm range (1 nanometer is one-billionth,  $10^{-9}$ , of a meter). Figure 1 shows a carbon nanotube structure. A typical carbon nanotube diameter is 1.3 nm, about 10,000 times smaller than a human hair diameter. Nanotechnology involves creating and using structures, devices and systems that have novel properties (physical, chemical, biological) and functions because of their small sizes.

Some nanomaterials have already moved from research labs into applications, and are already present in some sunscreens and toothpaste. Nanomaterials show potential in the aerospace, automotive, cosmetics, chemistry, food and medical sectors of industry. With enormous potential, there has been massive investment in nanotechnology resulting in a rise in the production of nanomaterials and a predicted future increase in consumer products relying on this technology.

The potential benefits of nanotechnology have been

widely circulated and appear to be well understood. The potential health hazards or risks these nanomaterials pose to researchers, producers, and eventually to consumers are not well understood. This paper is a survey of the current knowledge about the safety of nanomaterials. It is a compendium of knowledge gathered from articles listed in the references [Ref. 1-6]. No new research was performed in writing of the paper. However, the paper does present the information about safety risks from a system safety perspective, as a function of likelihood and consequence, instead of the toxicological approach. The paper focuses on carbon nanoparticles because they are widely used and have been developed at NASA laboratories. There has also been some limited safety research done on these particles. A word of caution, very few health studies have been performed for nanomaterials and even fewer have been replicated [Ref. 1].

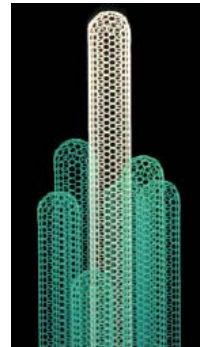


Figure 1: Carbon nanotubes.

### 1.1 Pathways

There are three major pathways for nanoparticles to enter the body: through the skin (dermal), through the respiratory system and through the digestive system (Figure 2). Although the skin serves as an important barrier for the human body, nanoparticles can penetrate the skin. The respiratory system allows intake of oxygen and the digestive system allows intake of water and food. The oxygen and nutrient exchange pathways in the lungs and intestines, respectively, allow nanoparticles to enter the human body [Ref. 2 and 3]. Like the skin, the eyes are a pathway for nanoparticles to enter the body. Potentially different barrier mechanisms are in place compared to the dermal system. Different consequences of ocular and dermal exposure may also be present. This pathway and the attendant consequences will not be addressed in this paper.

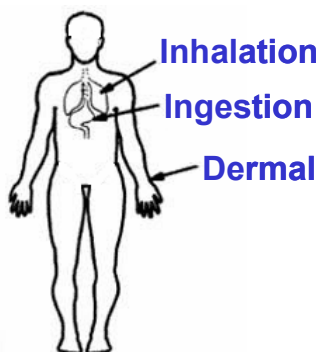


Figure 2: Major pathways for nanoparticles exposure.

### 1.2 Laboratory vs. Commercial Use

This paper discusses nanoparticle risk primarily from a laboratory safety perspective, where the primary issue is how to protect a laboratory worker from suspected nanoparticle hazards. This paper does not directly address the commercial use of nanomaterials in pharmaceuticals, food, cosmetics and other consumer products. In commercial use nanoparticles are ingested, inhaled, or applied on the skin deliberately, increasing the likelihood of nanoparticles entering the body. Some, but not all, of these commercial uses are governed by drug approval or product safety standards.

In comparison, nanoparticle production in the laboratory is typically done in a completely enclosed environment (i.e., reactors). This reduces the likelihood of exposure significantly. However, handling, processing of nanoparticles, cleaning of equipment and human error can lead to nanomaterial exposure.

### 1.3 Contaminants

As reference 1 points out, it is important to consider the total composition of the nanomaterial, including contaminants, in assessing the total risk from nanomaterials. In the laboratory a common contaminant is the catalyst used in creating the nanoparticles. Various catalysts are used for nanoparticle synthesis, the most common being iron, cobalt and nickel. The health effects of these contaminants should be considered in any risk assessment along with the health effects of the synthesized nanomaterial — typically, carbon.

The dermal exposure pathway for nanoparticles in the laboratory environment is schematically described in Figure 3. When nanoparticles are handled in the laboratory the skin may be exposed to these materials. The exposure is postulated to cause a local effect on the skin, typically dermatitis through mechanical irritation of the skin by nanofibers. The term postulated is used because it is currently unknown whether nanofibers cause dermatitis or even why some fibers are skin irritants and others are not [Ref. 2].

The outer layer of the skin consists of about 20 layers of keratinised, dead cells that are closely packed together and serve as a waterproof protective covering of the body [Ref. 4]. For most chemicals this outer layer is the rate-limiting barrier to penetration. In limited studies, penetration of nanoparticles into the skin has been shown to be size dependent — nano-size particles are more likely to enter deeply into the skin than larger particles [Ref. 3]. It is a complex phenomenon that may be material dependent and currently cannot be modeled. According to the review performed in Reference 3, there is no research suggesting that nanoparticles penetrating the skin can then be translocated to other body organs through the cardiovascular system. Since current knowledge is limited, this pathway in Figure 3 is shown in gray — the potential exists but is currently not established. If the particles did translocate to other organs then it would be important to study the effect of the nanomaterials on those organs.

### 2.1 Dermal Risk of Carbon Nanotubes in the Laboratory

Reference 5 assesses the exposure during handling of carbon nanotubes in the laboratory at four field sites. The authors analyzed iron and nickel (used as catalysts) as surrogates and found 0.2 to 6 mg of carbon nanotube material per gloved hand. Without a glove these nanomaterials would be deposited on the skin. In qualitative terms, without protective equipment the likelihood of exposure is high.

Once the material is on the skin, Reference 6 shows that exposure to carbon nanotube material of 0.06 to 0.24 mg/ml produces oxidative stress and dermal toxicity in human skin cells. The cell toxicity is associated with the iron used as a catalyst. Carbon, in non-nano studies, has been shown to cause carbon fiber dermatitis, hyperkeratosis, and nevi. Nano-size particles are speculated to be more toxic than larger particles [Ref. 6].

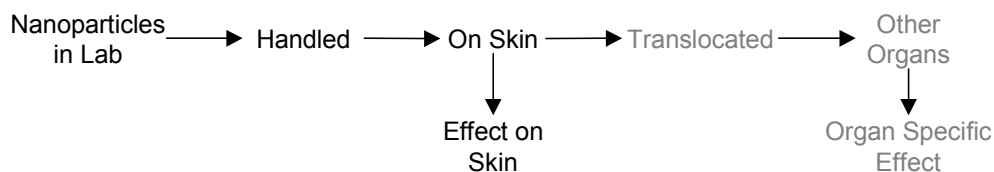


Figure 3: Dermal pathway for nanoparticles.

The current estimate of the qualitative risk of the dermal exposure pathway from carbon nanoparticles and its contaminants in the laboratory is a combination of high likelihood of exposure and a potential consequence of dermatitis.

### 3. INHALATION EXPOSURE

The inhalation exposure pathway for nanoparticles in the laboratory environment is schematically described in Figure 4. When nanoparticles are agitated in the laboratory they can form aerosols and be released into the air. There is no single, definitive characterization of aerosol release from nanomaterial powders; however, reference 5 found that it is difficult to form an appreciable amount of carbon nanotube aerosol. To keep the topic general, this paper assumes that nanomaterials can become airborne.

Laboratory personnel may inhale the aerosol-laden air. The air passes through the various respiratory structures until it reaches the lungs — by which time it has lost most of the large particles that it carried. The larger particles are deposited in the airways, while the smaller diameter particles (like nanoparticles) reach the alveoli. The alveoli are the main gas exchange area of the lungs — oxygen into the blood and carbon dioxide from the blood. In the alveoli, just two layers of cells separate the air from the blood [Ref. 4].

The local effect of nanoparticles on the respiratory system can occur anywhere from the nostrils to the alveoli. There is very little information about the local effect of nanoparticles on the respiratory system. Although some nanomaterial toxicity work has been performed on cells in the laboratory, these only indicate potential local effects. However, non-nano studies have shown that nickel (used as a catalyst) has been associated with increased risk of nasal cancer. Also, it is generally accepted that fibers that are not easily cleared from the lungs can induce pulmonary disease, and this may apply to nano-fibers as well.

The local effect on the respiratory system is a function of the deposition rate and clearance rate from the respiratory system. For larger particles deposited in the upper respiratory system, clearance is by the cilia-mucus escalator mechanism — particles are entrapped in the mucus and moved along by ciliary action into the larynx. From the larynx the mucus-entrapped particles are either coughed up or swallowed. Nanoparticles are likely to be deposited in the alveoli where the clearance mechanism is phagocytosis — particles are engulfed by macrophage cells that transport them either to the upper respiratory system or into the lymph nodes [Ref. 4]. This macrophage phagocytosis clearance mechanism is

relatively slow compared to the quicker cilia-mucus escalator clearance mechanism. Currently, there is limited knowledge about the macrophage phagocytosis clearance rate with respect to nanoparticles. The limited knowledge suggests that clearance is a function of the total amount of particles, particle size, and particle surface area [Ref. 2 and 3].

One cause for concern is that nanomaterials may be bio-persistent solid materials, like asbestos fibers or silica, remaining for years in the lungs and increasing the risk of developing chronic effects. Cell toxicity may be predicted by certain characteristics of the particle lodged in the alveoli. High cationic charge densities, highly flexible structures and the presence of surface radicals and reactive oxygen species tend to be more toxic to cells. These predictions are based on studies using non-nano particles. This may mean that nanoparticles with similar characteristics are more toxic to cells, but this must be verified [Ref. 2 and 3].

According to the reviews performed in References 2 and 3, there is new research suggesting that inhaled nanoparticles can be translocated from the lungs to other organs through the cardio-vascular system and the nervous system. Currently there is no information about the effect of inhaled, translocated nanoparticles on other body organs, so this path is shown in gray in Figure 4.

#### 3.1 Inhalation Risk of Carbon Nanotubes in the Laboratory

Reference 5 demonstrates that it is difficult to create an appreciable amount of carbon nanotube aerosol based on the laboratory work performed at four field sites. Only vigorous agitation led to significant nanoparticle aerosol generation and the concentration generated during handling was low — less than 53  $\mu\text{g}/\text{m}^3$  in all cases. In qualitative terms, the likelihood of exposure in the laboratory is low.

Three studies indicate that exposure to carbon nanotubes produce lung cell toxicity in rats and mice, but one author concluded that their findings might not be based on a cause-effect relationship [Ref. 3]. Like non-nano fibers, carbon nano-fibers that are not easily cleared from the lungs may induce pulmonary disease.

The current estimate of the qualitative risk of the inhalation exposure pathway from carbon nanoparticles and its contaminants in the laboratory is a combination of low likelihood of exposure and no clear evidence for any consequence. However, as is true of any new field, the consequences are better judged after nanotechnology has had time to establish itself and more studies have been performed on their toxicological effects.

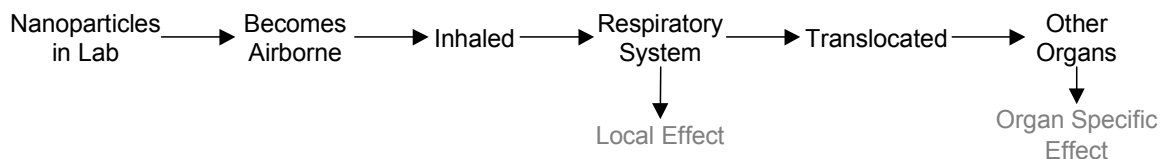


Figure 4: Inhalation pathway for nanoparticles.

#### 4. INGESTION EXPOSURE

The ingestion exposure pathway for nanoparticles in the laboratory environment is schematically described in Figure 5, and looks very similar to the inhalation pathway. Although unlikely, nanoparticles handled in the laboratory could be inadvertently ingested.

The ingested particles pass through the various parts of the digestive tract — mouth, throat, esophagus, stomach, small intestine, large intestine, and then eliminated through the anus. The local effect of nanoparticles on the digestive tract can occur anywhere along this path. However, this review did not find any literature about the local effect of nanoparticles on the digestive system.

Ingested particles are generally absorbed from the gastrointestinal tract depending on particle size and surface charge. Smaller particles and anionic particles are predicted to penetrate quicker through the lining of the digestive tract, enter either the blood stream or the lymphatic system and can then travel to various organs [Ref. 2 and 3]. Reference 3 states that in general, the intestinal uptake of particles is better understood than inhalation or dermal exposure. Reference 2 states that nanoparticles that have been added to processed food have so far shown no observable adverse effects.

##### 4.1 Ingestion Risk of Carbon Nanotubes in the Laboratory

The ingestion exposure pathway from carbon nanoparticles and its contaminants in the laboratory is a combination of very low likelihood of exposure and no clear

evidence for any consequence. However, the consequences are better judged after nanotechnology has had time to establish itself and more studies have been performed on their toxicological effects.

#### 5. DISCUSSION

The surveyed papers propose that because nanoparticles vary in their chemical composition and biological and immunological properties, the risks posed by them also vary. A better understanding of the risk needs to be developed not only for carbon nanoparticles but also for other nanomaterials. Each nanomaterial should be treated individually with respect to expected health risks.

Assuming no protective equipment, the estimate of the qualitative risk of the various exposure pathways from carbon nanoparticles and its contaminants in the laboratory are:

- Dermal — a combination of high likelihood of exposure and a potential consequence of dermatitis.
- Inhalation — a combination of low likelihood of exposure and no clear evidence of any consequence.
- Ingestion — a combination of very low likelihood of exposure and no clear evidence of any consequence.
- Ocular — not addressed in this paper.

At present there are no regulations regarding nanotechnology. More studies need to be performed before regulations can be established. In the mean time, a cautious approach of wearing protective equipment is suggested for nanomaterial researchers in the laboratories.

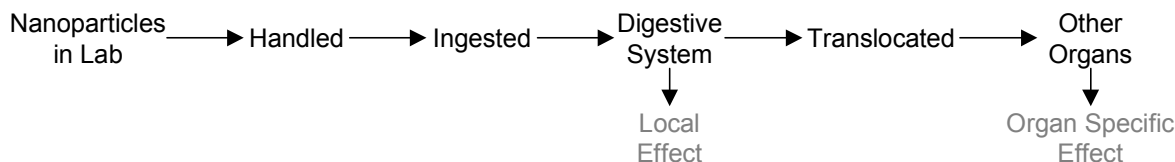


Figure 5: Ingestion pathway for nanoparticles.

#### 6. ACKNOWLEDGMENT

The author would like to thank Dr. Stacy Budin for her effort in reviewing and editing of this paper. Additional reviews by Doug Smith, Rebecca Averill, Darvin Heer and Joe Dzekevich improved the paper.

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