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How Nanoparticles Enter the Human Body and Their Effects There

Summary

Nanomaterials have a wide range of applications, leading to highly diverse exposure scenarios for humans. This calls for an analysis of how nanoparticles enter the human body and what health hazards they pose there. Current evidence indicates that the smaller the nanoparticles, the more pronounced their toxic effects. Beyond size, however, the shape and chemical composition of nanoparticles contribute to their biological impacts. Nanoparticles are known to induce inflammation in the lung, and some reports of pulmonary fibrosis are available. There are indications that nanoparticles penetrate vascular tissue and therefore trigger certain dysfunctions or influence the cardiovascular system. One recent study involving an animal model demonstrates that needle-shaped, asbestos-like nanotubes can induce chronic inflammations. Only few data are available on effects on the digestive tract and the nervous system or on the uptake into the bloodstream via the skin. This contribution presents the key data and outlines the potential pathways by which nanoparticles can enter the human body.

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Introduction

Nanotechnology and the respective nanomaterials are employed in the research sector and also contained in many commercially available products. This means that the general public is currently being exposed to nanomaterials. This raises the question whether such materials enter the human body and whether they can trigger health effects. The potential health risks are poorly investigated. A number of studies have reported that free nanoparticles, due to their small size, can penetrate into the finest lung structures by breathing, can cause inflammatory reactions, and subsequently can enter the bloodstream. The circulatory system distributes such particles throughout the body, where they can enter other organs. Nanoparticles can also be actively or passively incorporated in cells, and harmful effects cannot be excluded. The biological effects are not based on chemical composition alone: size, shape, surface texture, aggregation state and surface charge also play an important role. The present dossier examines the potential entry sites of nanoparticles into the human body and describes several biological effects which can be triggered.

Entry sites into the human body

Nanoparticles can enter the body directly through body openings, for example by inhaling or swallowing. There is also an ongoing discussion about a potential indirect uptake through the skin pores. The human skin, the gastrointestinal tract and the lungs are always in direct contact with the environment. Whereas the skin serves as a barrier, the gastrointestinal tract and lungs allow the (active or passive) transport of various substances such as water, nutrients or oxygen. It seems likely that nanoparticles can also enter the human body via these routes. Due to their small size, such particles can penetrate the cell membrane and show activity at the subcellular level. How this takes place is currently being investigated.

The skin

The human skin is a true barrier against the environment (except for solar radiation, which is essential for vitamin D production); no essential elements are absorbed through it. The human skin has an average surface area of 1.5-2 m^2, whereby the uppermost layer consists of a relatively thick layer of dead cells (so-called keratinized cell layer, 10 µm) (Fig. 1)[1].

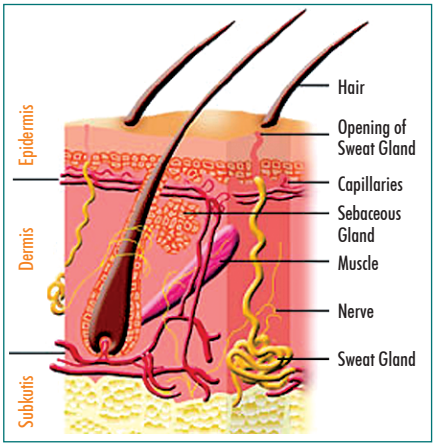

Figure 1:
Structure of the human skin[1]

Nanoparticles composed of titanium- or zinc oxides are currently contained in a wide range of cosmetic products such as sunscreen lotions, where they function as highly effective UV-absorbers. This raises the question whether these products or the nanomaterials penetrate the upper skin layers and enter underlying tissue. To date, there is no concrete evidence to support this scenario. Nonetheless, there are indications that such particles can accumulate around the hair roots, in the so-called hair follicles. During hair growth, these follicles are open: this would provide a route for nanoparticles to reach deeper layers. Studies have shown that the components of particle-free lotions that have been rubbed in are completely absent in the hair follicles after 7 days, but that the number of particles in the nanoparticle-containing lotion only dropped by half. No uptake into the blood (translocation) through healthy skin has yet been demonstrated.

In contrast, studies on healthy skin have shown that various so-called quantum dots can penetrate the skin. (Quantum dots are produced from semiconductor materials and absorb certain wavelengths of light. In life sciences they find use as biomarkers, or also in LEDs and displays.)

Research is currently being conducted on whether particle uptake differs in injured or diseased skin (psoriasis etc.). There is consensus, however, that the barrier function is compromised and nanoparticle penetration possible.

The digestive system

The entire gastrointestinal tract is in direct contact with all ingested materials, and all the necessary nutrients for the body (with the exception of gases) are absorbed here. The whole surface of the gastrointestinal tract serves as a complex barrier; at the same time, it is the key gate for the macromolecules the body needs. Only small molecules can diffuse through the stomach epithelium. The epithelium of the intestine is in immediate contact with the partially digested material, enabling direct nutrient absorption. The food in the small intestine is already digested and consists of a mixture of molecules such as disaccharides, peptides, fatty acids and monoglycerides. These are converted in the intestinal villi and then absorbed (Fig. 2)[7]. In order to increase the surface of the epithelium, the intestinal villi are further covered by even smaller villi (microvilli). This yields a surface of about 200 m^2 for nutrient uptake in the gastrointestinal tract.

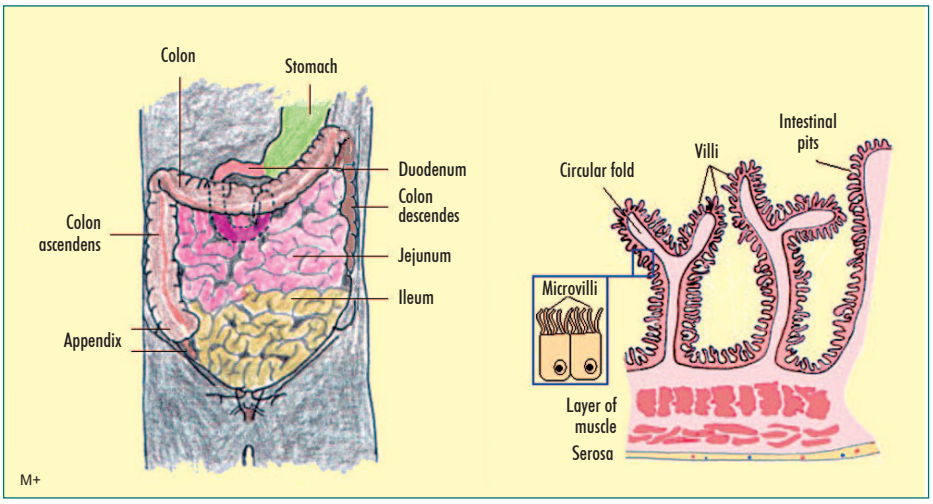

Figure 2: Structure of the human gastrointestinal tract. (Left: overview right: enlarged view of the mucous lining of the gut along with the microvilli[7])

Nano-scale structures can involuntarily enter the gastrointestinal tract with food or when swallowing material cleared from the bronchi via mucociliary clearance. The oral intake of an average person is estimated to be 10^{12} to 10^{14} nano- and microparticles daily[8], with the overwhelming majority being silicates and titanium dioxide. In animal experiments, 50-100 nm-sized polystyrene particles pass through the gut wall and enter the lymphatic system[9]; fullerenes, in contrast, tend not to be absorbed. Other studies, however, show no uptake into the vascular system via the gastrointestinal tract[10,11]. There is clearly no consensus about how nanoparticles behave in the gastrointestinal system. One study examined the uptake of radioactively marked, intravenously injected fullerenes compared with uptake through the gastrointestinal tract in rats. However, 98 % of the orally ingested material was excreted, whereas about 80 % of the intravenously injected material was deposited in the liver after one week[12]. This is evidence that nanoparticle uptake via the gut could play a subordinate role. Only few studies have examined the uptake and residence time of nanoparticles in the gastrointestinal tract, hindering definitive conclusions.

The lung

The lung consists of two different functional areas, namely of the respiratory tract, where air is transported into or out of the lung, and the gas exchange area (bronchi, bronchioli, alveoli), where oxygen and carbon dioxide are exchanged with the environment. The human lung consists of about 2300 kilometers of respiratory tract and about 300 million alveoli (Fig. 3)[13]. The surface area of the human lung is nearly 140 m^2 and represents an enormous exposure surface. The respiratory tract functions as a relatively ro-

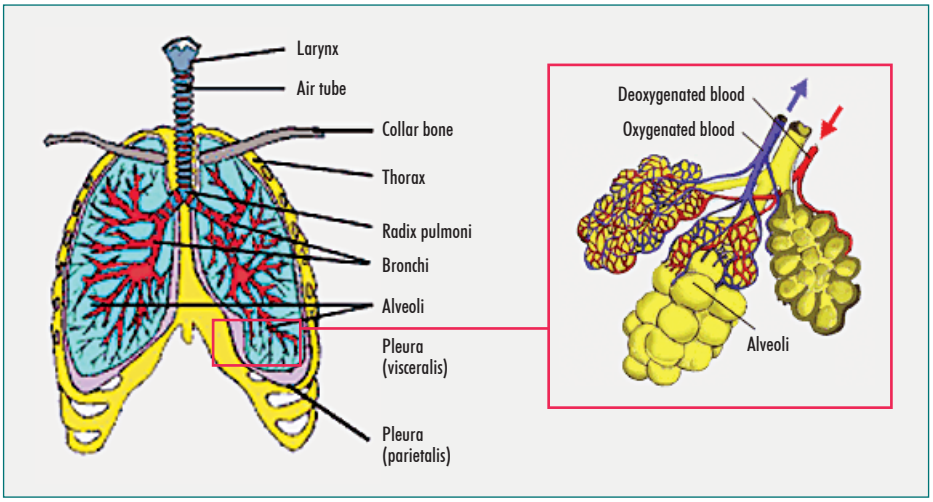

Figure 3: Structure of the human lung. (Left: overview; right: enlarged view of the alveoli[13])

bust barrier consisting of an active epithelial layer that is protected by a viscous mucus layer (air-blood tissue barrier). In the gas exchange area, the barrier between the alveolar wall and the capillaries is very thin. The air inside (in the lumen) of the alveoli is only a few nanometers away from the flowing blood. Animal experiments show that nanoparticles can cross this air-blood tissue barrier. This introduces nanomaterials into the body's circulatory system[14]. Due to the large surface area of the alveoli and the intensive air-blood contact, the alveoli are more exposed to environmental influences than is the respiratory tract. The bronchi are coated with a mucociliary layer that removes particles deposited in the lungs (mucociliary clearance). This mucociliary clearance is sufficient to remove most of the nanoparticles deposited along the bronchi. The effectiveness of this mechanism, however, decreases as particle size decreases. This means that nanoparticles enter the alveoli and are deposited on the epithelium, after which a direct exchange with the alveolar epithelia can take place. So-called feeding cells (macrophages) take over the task of removing foreign bodies because the alveoli lack a mucociliary clearance mechanism.

The minute size of the particles plays a key role here as well. Animal experiments demonstrate that the normal cleaning mechanisms can fail because insoluble nanoparticles can be deposited for months to years in the bronchi and alveoli[15]. Higher deposition rates have been reported in patients with chronic bronchitis and bronchial asthma, whereby the reduced clearance and the elevated breathing rates in these patients have been discussed as causes[15,16].

How long the absorbed nanoparticles remain in the body (kinetics) remains unknown. Some studies indicate that, after inhaling the nanoparticles, these can enter other organs. Thus, after 7 days, inhaled nanoparticles were detected in the liver, spleen, brain, kidneys, heart and bone marrow[12,17]. A metabolization of absorbed inorganic nanoparticles (for example titanium dioxide) appears to be unlikely, whereas organic nanomaterials (e.g. fullerenes) are more likely to be modified by metabolic processes. Whether the particles translocate into the lymphatic/blood circulation and become distributed and potentially accumulate in the body, and whether they affect the cardiovascular system, is the subject of ongoing study.

Research is also being conducted on whether particles that reach the brain via breathing, for example by way of the olfactory nerve, remain in the brain and potentially accumulate there[18,19]. Nanoparticles have also been demonstrated to penetrate into higher brain centers though this route (cortex, thalamus and cerebellum), with electroencephalograms showing an altered pattern.

Effects on the human body

Animal experiments demonstrate that inflammations of the bronchi and alveoli can be triggered by nanometer-sized carbon-, polystyrene-, iron-, titanium dioxide- and iridium particles[17,20]. In individual cases, inflammatory reactions in occupationally exposed persons have been described for nanoscale indium-zinc-oxides[21] and zirconium particles from welding fumes[22].

A range of data is available on the effects of nanoparticles, whereby a close correlation exists between surface texture and biological effects. In rats and mice, for example, titanium dioxide (or nickel- and vanadium dioxide particles) measuring 20 nm administered directly into the lungs triggered stronger inflammatory reactions than 250 nm particles. These and other results show that toxicity is influenced more by the surface than by mass[12]. Moreover, beyond the size of the surface, its features (for example the presence of reactive groups on the surface) determine the toxicity. In a special mouse model, a recent pilot study shows that intraperitoneally administered (area of the body covered by peritoneum), long (ca. 20 µm), needle-shaped nanotubes can trigger chronic inflammation, while short and/or curved nanotubes induce no such effects. Since their features (form, length and insolubility) resemble those of asbestos fibers, a comparable mechanism of action has been discussed[23].

A key issue is a potential carcinogenic effect of inhaled nanoparticles. The administration of high doses of granular and biologically stable nanodust (inert bulk material) in rats was shown to be correlated with an elevated tumor frequency[24]. It remains unclear, however, whether this involves a direct genotoxic effect of the nanoparticles or whether it reflects secondary reactions such as the release of free radicals, as is the case in chronic inflammations. The question of how small amounts of nanoparticles behave in humans and whether they can induce cancer cannot be answered at this point. There is also uncertainty about what happens with the absorbed particles. Some are taken up (internalized) by epithelial cells, as has been described for nano-scale titanium dioxide, gold, polystyrene and zirconium)[22,25]. The underlying explanatory model states that the released free radicals possibly trigger so-called oxidative stress and irreparably damage the cells (cytotoxicity). Other authors discuss the potential deposition of the nanoparticles directly onto the DNA, which can lead to a genotoxic effect[20]. Absorbed nanoparticles can translocate from the lung into the blood[10,14,27,28], whereby these results are being hotly debated. There is agreement that, beyond the size of the particles, their surface texture and charge or coating can influence the biological effectivity[12,15].

Conclusions

Nanoparticles with a diameter of up to 100 nm, such as carbon or metallic oxide particles, are already present in the environment. They can induce biological effects via cell membrane penetration and are more reactive than larger particles. The use of nanoparticles, however, can improve the efficiency of cosmetic products for example, and makes it possible to create new coatings (e.g. scratch-proof paints). Moreover, they are considered as candidates for new and promising medical applications and therapies. The increasing use of nanoparticles, however, calls for further research in order to be able to conduct risk assessments. In particular, it is important to investigate the actual exposure of different groups such as consumers, occupationally exposed persons, and patients as well as both users and producers of nanoparticles. In addition, the material uptake mechanisms need to be investigated for a better understanding of the effects.

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