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Health Risks of Nanotechnology

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ABSTRACT

Nanotechnology is one of the key technologies of the 21st century and is associated with high expectations. Products with completely new properties for application in medicine, science, industry and various techniques are designed. However, the larger surface area of nanoparticles makes them highly reactive compared to larger sized particles of the same chemistry resulting in both, desirable and undesirable effects. The need for toxicological data has become increasingly important, thus several international projects are ongoing throughout the European Union. The question concerning the risks for the health and environment should not be disregarded.

INTRODUCTION

In most cases, nanotechnology is based on nanoparticles, which can be defined as solid colloidal particles ranging in size from 10 nm to 1000 nm. The unique power and potential of nanotechnology at this nano-scale include changes in the material's optical, magnetic, and electric properties, so-called quantum effects. However, for many years humans have been exposed to such nano-sized materials, for example, fullerenes derived from combustion processes of volcanoes, industrial dust, and fires, before engineers started working with nanomaterials. Nowadays, health risks are believed to be the most critical aspect of nanoparticles, although these materials are applied in many consumer products without any specific approval. In this context, the latest Temas Report has summarized the current resources of public information regarding this area [1]. Our review is based on these data and focuses on applications for consumer products, the current knowledge of particle uptake and on recent European Union (EU) research activities in this field.

The benefits of nanotechnology have been wildly published, with consumer products increasing in the food and cosmetics industries, in industrial production as well as in nanomedicine. Occupying an important position in the risk assessment of nanomaterials is the field of nanomedicine. Many new applications of nanomaterials have been developed for diagnostic and therapeutic purposes but the chemical and physical properties that make nanoapplications attractive can also lead to

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potential side effects on the human body. In the case of nanomedicine, it always depends on the severity of disease whether one wishes to accept the possible risks of a nano-based treatment. Nevertheless, currently, the knowledge of the toxicology of nanoparticles, and more recently of nanotubes, is poor [2-4].

Table 1 lists a collection of reports concerning nanotoxicology, as published by different organizations, both private and public.

Traditionally, the systematization of nanotechnology has been based on four technologies: biotechnology, chemistry, physics, and semiconductor technology. More recently, the British physicist Richard Jones suggested classifying nanotechnology according to its novelty of utilization in comparison to precedent technologies. Accordingly, he distinguishes between the incremental and the evolutionary nanotechnology [36, 37]. This description of systematization however, excludes potential risks and public discussion. Thus, Niels Boeing, physicist and scientific journalist, suggested to include risk discussion and therefore categorize nanotechnology into three groups:

- isolated nanotechnology
- bioactive nanotechnology
- disruptive nanotechnology

Isolated nanotechnology consists of nano-components that are embedded and isolated from the environment. In this context, disposal and recycling of isolated materials is not discussed because if these processes took place, the materials would then belong to the bioactive group.

The second group is subdivided into unintended and intended bioactive nanotechnology. It includes synthetic nanoparticles, buckyballs, and nanotubes. The intended bioactive nanotechnology deals with nanoparticles used in nanomedicine, clinical investigations, and the food industry.

Finally, the disruptive nanotechnology deals with the so-called "nanorobots", which theoretically are microscopic devices measured on the scale of nanometers. They hold potential applications in the assembly and maintenance of sophisticated systems. Nanorobots might function at the atomic or molecular level to build devices, machines, or circuits. In a process known as molecular manufacturing, they would perform tasks in both the medical and industrial fields. In order to prevent fraudulent use of this group, a moratorium should be deployed [37].

NANOTECHNOLOGY AND POTENTIAL RISK TO THE HUMAN HEALTH

There is a substantial need for a vehicle that can efficiently carry biological ingredients to the site of

Table 1a: Reports by Private Organizations

Report	Organization	References
ETC Report	ETC Group	[5, 6]
Greenpeace Report	Greenpeace Environmental Trust	[7, 8]
Cientifica White Paper	Cientifica Ltd.	[9]
Allianz Report	Allianz AG	[10]
VDI Report	VDI GmbH	[11]
Swiss Re Report	Swiss Re	[12]
Basics Reports	Basics AG	[13]

Table 1b: Reports by Public Organizations

Title	References
Informed public perceptions of nanotechnology and trust in government	[14]
Relative risk analysis of several manufactured nanomaterials	[15]
Report of the Royal Society and Royal Academy of Engineering	[16, 17]
Nanotechnology and the poor: Opportunities and Risks	[18]
Nanotechnology and Risk	[19]
Research Report for the Health and Safety Executive	[20]
Towards a European Strategy for Nanotechnology	[21]
Centre for Nanoscale Science and Technology, Rice University Report	[22, 23]
Reports from the Department of Environmental Medicine	[24-33]
Reports from the DuPont Haskell Laboratory	[34]
Review on Technical Aspects of Nanotoxicology	[35]

their action within the human body. Due to the size of nanoparticles, they are able to cross different barriers, for example, cell membranes or the blood brain barrier [38], making them an appropriate transport system for drug delivery. Furthermore, they protect the drug molecules and are able to prolong the biological effect. Research is being conducted to design vehicles that are responsive to signals inherent within the body [39, 40].

Potential Applications of Nanoparticles

Table 2a: Inorganic Materials [41]

Material	Formulation	Application	Advantage of Nano	References
TiO_2	Particle, Coating	Sunscreen, Cosmetics, chocolate	UV-Absorption, Transparency	[42, 43]
ZnO	Particle	Sunscreen, Cosmetics	Transparency, High surface	[42]
Al_2O_3	Particle, Membrane	Transparent Hardcoats	Hardness	[44]
SiO_2	Particle, Coating, Powder	Transparent Hardcoats, Ketchup	Small Particle-size	[43, 44]
ZrO_2		Nanofiltration, catalytic converter	High surface	[42]
CeO_2	Particles in polymers	UV-Absorption	Smooth Surface	[45]
Phyllosilicates	Composite	Transparent Polymers		[46]
Zeolite	Particle	Catalyzer with higher selectivity	High Surface	[42]

Table 2b: Metals and Carbon Materials

Material	Formulation	Application	Advantage of Nano	References
Pt, Ir, Zn/Pd Fe/Ag	Particle	Wastewater treatment, Filler in vulcanized rubber	High Surface, High Reactivity	[47]
Ni, FeO	Coating	Hyperthermia		[42]
Carbon black	Filler in vulcanized rubber	Tire	Abrasion Resistance	[48]
Fullerene	Particle, Membrane	H_2 Accumulator	High Surface, High Selectivity	[42]
C-Nanotubes	Single walled Nanotubes			[42]
Diamond-like Carbon	Coatings			[42]

Table 2 presents a summary of known nanomaterials used in industrial processes, consumer products, and the environment, and relevant studies about their harmful effects.

Portals of Entry of Nanoparticles into the Human Body

Humans are exposed to nanoparticles through various routes: inhalation via the respiratory tract, dermal absorption/penetration through hair follicles, ingestion by the gastrointestinal tract, and injection.

Table 2c: Polymers and Hybrid Materials [41]

Material	Formulation	Application	Advantage of Nano	References
Organic Block-copolymeres	Dispersion	Paint		[49]
Organic Polymere	Nanofibre	Textile	Small Pore size	[50]
Dendritic Polymeres	Membrane, Particle	Ultrafiltration, Controlled-Release-System/Cosmetics		[42, 51]
Inorganic- and Organic Hybridpolymers	Coatings Composite with Filler	Ceramic, Eyeglasses. Dental Material	Transparency Consistency Consistency	[52] [53, 54]

Nasal Absorption

Nanoparticles deposit on the nasal mucosa only if the inhaled particles consist as aggregates larger than 50 µm. Another option is through liquid droplets, also larger than 50 µm, in which the nanomaterial is dispersed. Both technologies, solid as well as liquid aerosols, are effective delivery routes underlined by their use in drug industry. The current focus lies in the research of mucosal vaccines, an attractive delivery system for inducing a protective immune response. Additional applications involve the nasal administration of proteins and peptides [55, 56].

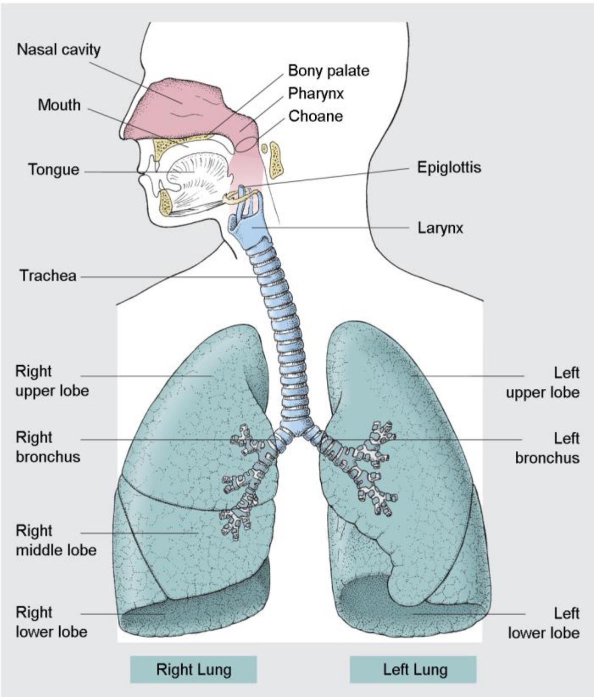

Fig. 1: Portals of Entries for Nanoparticles [32]. Nasal, tracheobronchial, and alveolar regions where nanoparticles can deposit following inhalation. Reprint and modification with permission from Huch / Jürgen: Mensch Körper Krankheit, 5.A.
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Beside these wanted medical applications, most published studies however, deal with the toxicological risks of nanoparticles following non wanted inhalation into the lungs. Special investigations of the toxicological risks for the nasal mucosa, arising from the environment, have not yet been conducted. Nevertheless, potential risks have to be taken into consideration concerning allergies as well as for the neuronal connection between the brain and the olfactory bulb. For solid nanoparticles this process has not been investigated until now [57].

Currently, there are only a few studies that describe the translocation of nanoparticles into the brain [30]. According to new reports from the University of Rochester, Department of Environmental Medicine, the uptake of nanoparticles via the olfactory route seems to be significant. Investigations on rats, which are nose breathers, showed that the inhalation of Manganese dioxide particles with a size of 30 nm increases the Manganese dioxide concentration up to 3.5-times in the olfactory bulb [58].

Long et al. describe in their study the influence of TiO_2 on the central nervous system. TiO_2 nanoparticles are used in air and water remediation as well as in many products designed for direct human use and consumption. Subsequent to photo-activation, free radical particles of TiO_2 are released, which results in possible risks to biological targets. In their study, brain microglia of mice were exposed to TiO_2 nanoparticles (25–30 nm) and the cellular expressions of reactive oxygen species was measured. The effects showed that mouse microglia respond to TiO_2 nanoparticles with cellular and morphological expressions of free radical formation [59]. Interpretations of these results indicate that perhaps nanoparticles (such as currently present in sunscreens, see Dermal Absorption) may stress brain cells.

Currently, TiO_2 nanoparticles found in sunscreens are larger than 30 nm. Most substances applied onto the skin have a particle size of approximately 200 nm and recent investigations showed that particles of this size could not be found in the dermis of healthy skin.

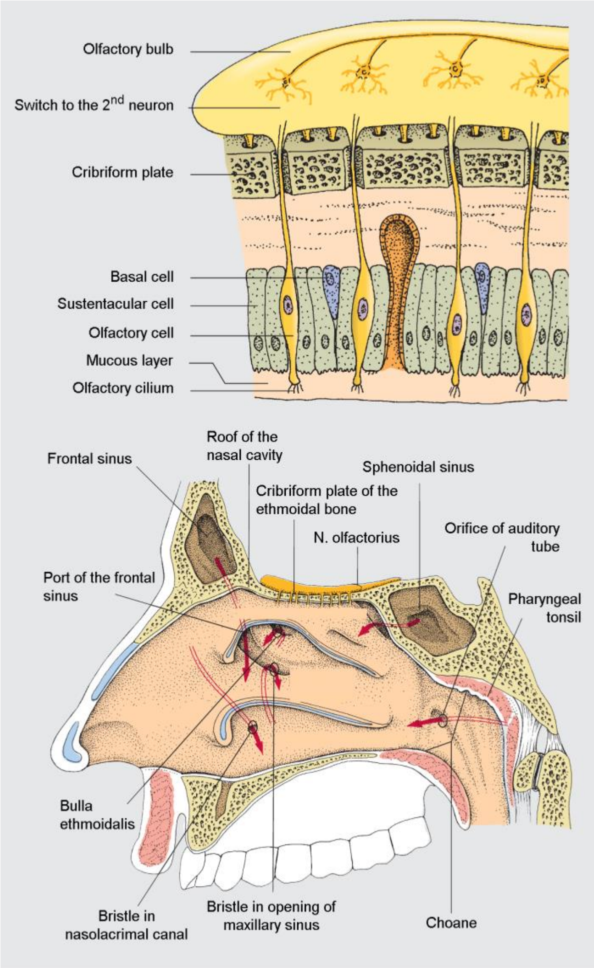

Fig. 2: Nasal absorption: Schematic representation of the nose and the olfactory bulb, the neuronal connection to the brain. Nanoparticles can be taken up by the nerve endings of the olfactory bulb and may be translocated to the central nervous system. Reprint and modification with permission from Huch / Jürgen: Mensch Körper Krankheit, 5.A.
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Pulmonary Absorption

Variable-sized nanoparticles produce different effects depending on the portion of the lung in which they settle. The smaller the particle, the higher is its probability to be transported into the lung. Particles smaller than 2.5 microns can reach the alveoli, while those with a diameter of 0.1-1 µm are deposited mainly in the alveolar region. Exhalation of particles becomes possible when their diameter is far smaller than 0.1 µm, which also depends on their aerodynamic properties. Therefore, their deposition in the lung is limited (see Fig. 3).

The mucociliary escalator is responsible for the clearance of the upper airways. This system is composed of mucus-producing cells and cilia, tiny hair-like projections. The mucus, which covers the airways, traps incoming dirt particles which are then propelled by the cilia towards the anterior portion of the nose or down the throat to be removed from the airway. The clearance of the lung's alveoli is conducted through phagocytosis, resulting from the activation of macrophages [38, 60].

The deposition of nanoparticles is subjected to three mechanisms:

- Impaction
- Sedimentation
- Diffusion

Nanoparticles can be taken up by many types of cells through "non-specific interactions" with the cell membrane followed by phagocytosis or pinocytosis. If these particles are incorporated into pulmonary macrophages the possibility exists that a cascade of immune reactions will ensue. Depending on the nanoparticle material, inflammation of the respiratory tract could lead to tissue damage and systemic effects. Furthermore, the transport of nanoparticles through the bloodstream to other vital organs or tissues seems possible following pulmonary absorption, which may result in cardiovascular and extra-pulmonary effects [38].

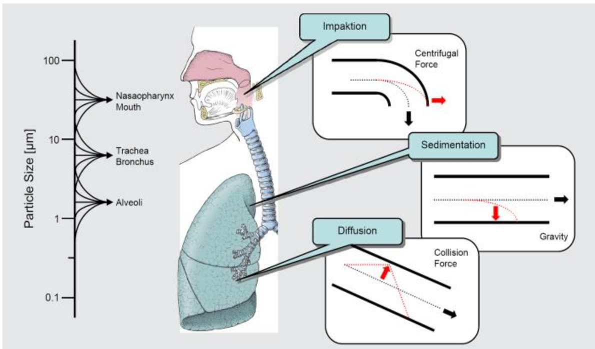

Fig. 3: Pulmonary deposition of nanoparticles

The nanoparticles' cytotoxic effect is probably due to their surface properties and electrokinetic potential. As their size decreases, the particles' surface becomes highly reactive and their toxicity increases. Particles not incorporated into cells and eliminated by macrophages deposit in the interstitium and "overload" the lung's defenses.

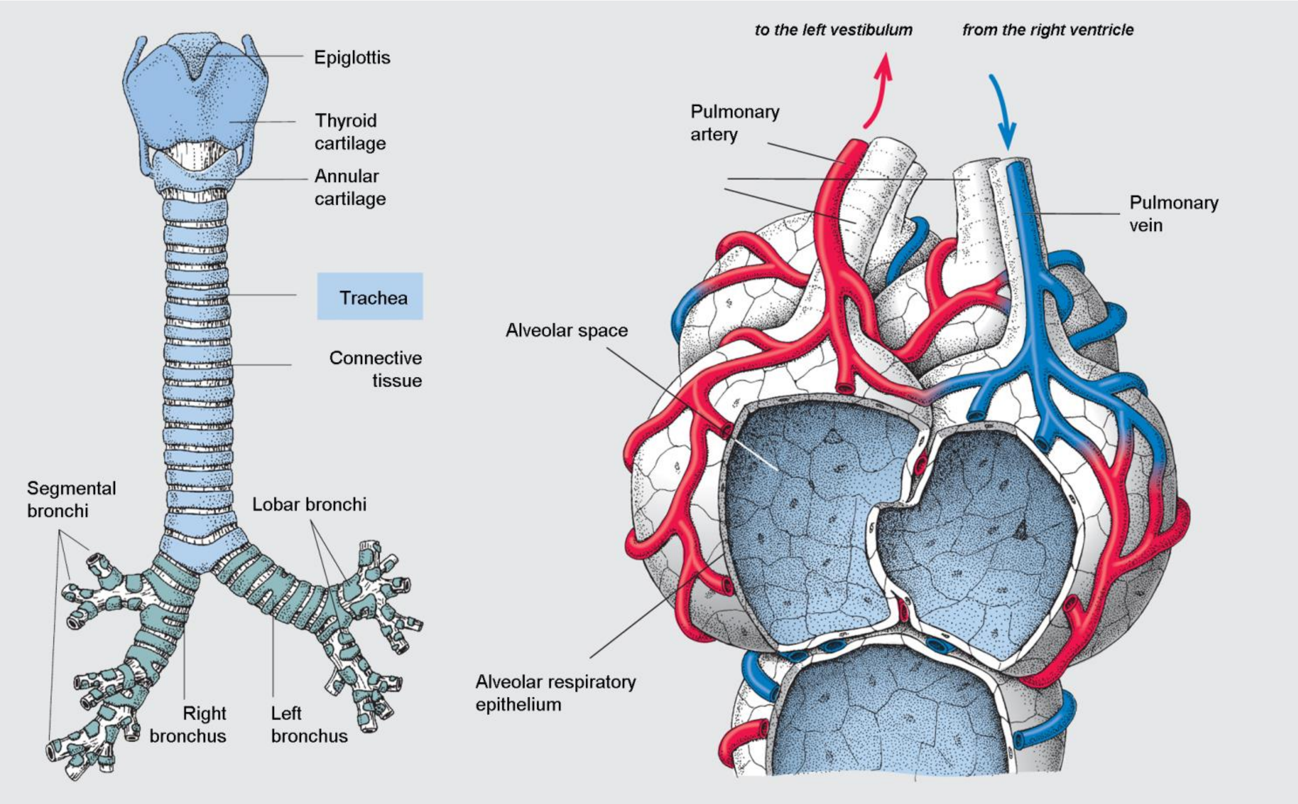

Fig. 4: Pulmonary route of nanoparticle deposition: Inhaled nanomaterials pass primarily the trachea (left side) and depending on the size, the surface, and the aerodynamic properties, nanoparticles can deposit in the alveoli (right side). Reprint and modification with permission from Huch / Jürgen: Mensch Körper Krankheit, 5.A.
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This overload leads to oxidative stress reactions and inflammation. In addition, free radicals are also generated leading to oxidative damage. This process can be compared to the clinical picture of asbestos fibers, which deposit in the alveoli and prevent the gas exchange [61].

The elimination of nanoparticles from the lung depends on the total mass, the size and the particle's properties. With decreasing size, fewer nanoparticles are eliminated from the lung, which can even result in translocation into the interstitium and lymph nodes [62]. Quartz particles in particular can cause serious lung diseases. Toxicological studies have shown that even low level exposure to micrometer-sized particles of quartz causes lung inflammation, cell death, fibrosis, and tumors in rats. Other effects include atherosclerosis and heart disease. Inhaled nano-fibers and nanotubes can also enter the alveoli and are much more toxic than nanoparticles [34, 38, 55, 56, 63, 64].

Dermal Absorption

The skin is an essential organ and an important barrier, protecting the body against environmental insults. It contains a variety of nerve endings that react to cold and heat, touch, pressure, and tissue injury. The acidic film on the surface is composed of a mixture of lipids, sebum and sweat, providing the skin resistance against heterogeneous contaminants as well as bacterial and mycotic microorganisms. The skin regulates temperature and evaporation as well as acts as a storage center for lipids and water. Different drugs can penetrate through the skin, thus it is also an important site of uptake prior to the drugs' transport to other organs [65].

The skin is made up of the following layers: The epidermis, dermis (corium), and subcutaneous layer (Fig. 5). The dermis, located beneath the epidermis, consists of connective tissue and is separated from the epidermis by a basement membrane. It contains hair follicles, sweat glands, apocrine glands, and blood vessels. Possible entry routes for nanoparticles to reach the bloodstream include absorption through the epidermis or directly via hair follicles [65].

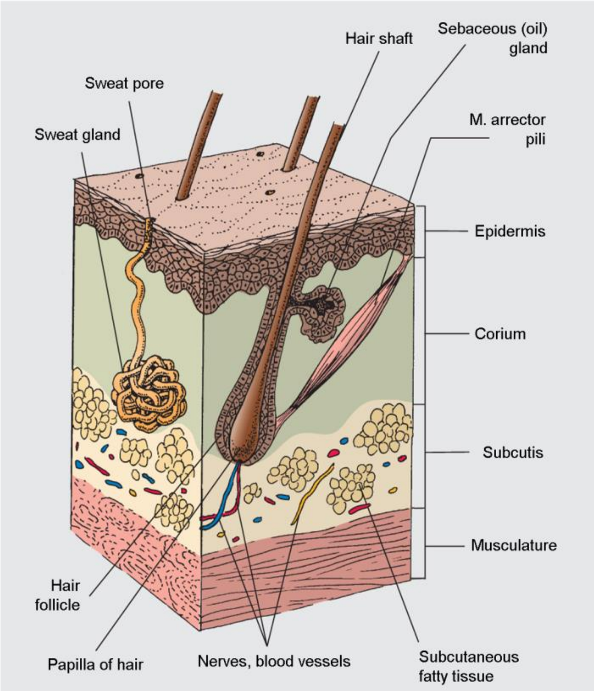

Fig. 5: The penetration of the skin and the absorption of nanoparticles can follow different routes: intercellular and transcellular penetration into the stratum corneum (epidermis) is possible as well as via hair follicles. The optimal size of nanoparticles for storage and penetration is 300-700 nm. Current investigations showed no penetration of nanoparticles of this size into the living dermis or subcutaneous layer [66]. Reprint and modification with permission from Huch / Jürgen: Mensch Körper Krankheit, 5.A., © Elsevier GmbH, Urban & Fischer Verlag Munich, Germany

The number of published studies concerning the risks of nanoparticles following topical application has been meager thus far. Long term studies have not been carried out and most of the investigations were made in unperfused skin. Generally, the penetration of nanoparticles into the skin depends on their size; as their size decreases, the likelihood that they will reach the dermis increases. The existence of additional pathways through the skin remains a moot question [36, 61].

Apart from environmental pollution by carbon black, silica, and so on, the skin also comes into contact with cosmetic products. Sunscreens, for example, consist of three main ingredients: oil, water, and ultraviolet-filtering substances. Until now, organic filters have been used to absorb ultraviolet (UV) rays and protect the skin against sunburns and DNA damage. Disadvantages of these filters include possible allergic reactions and deficient sunscreen. Zinc oxide and titanium oxide are particulate mineral sunscreen ingredients that are also capable of absorbing or reflecting a broad-spectrum of UV irradiation. Particulate substances of a certain size however, pose a certain "cosmetic" issue because following their application onto the skin they will leave a white film due to the reflection of the light. In order to solve this problem, thus making the sunscreem "invisible", the size of the particles has to be minimized to a nanoscale of 80-200 nm. Much smaller particles (15-20 nm) are also under investigation. As previously mentioned, when materials reach the nanoscale, they often no longer demonstrate the same reactivity as the bulk compound. In addition, with a decreasing size, the risk increases that below a specific size range the nanoparticles insignificantly scatter short wave light and therefore, would not possess any effective sunscreen properties [67].

As mentioned above, titanium dioxide nanoparticles are able to reach the stratum corneum (epidermis) and penetrate the skin via hair follicles [68]. At present, it is impossible to predict the behavior of nanoparticles in the skin [69]. Thus the question arises about deposition, biodegradation, as well as translocation to the brain, as previously mentioned, and long-term toxicological effects. In line with the Nanoderm Project (see Research Programs) titanium dioxide nanoparticles were also found in the stratum granulosum but hardly in the dermis. However, these investigations were only conducted on healthy skin. Research on sunburned and injured skin are currently unavailable [70, 71]. Interactions with the immune system are also disputed. However, it has been shown that the application of nanotubes causes allergic dermatological reactions [8, 38, 72-74].

A new source and application for nanotechnology is the textile industry. It will pave the way for new and improved functions of textiles such as water and mechanical resistance, antibacterial and fungicidal effects, and heat proofing [50]. In this case too, the question about the reactions of the nano-textiles with the skin remains open.

Per Oral Mucosal Absorption

The gastrointestinal tract is a complex barrier and the most important portal of entry for macromolecules. Possible ways for nanoparticles to reach the gastrointestinal tract include: water, food, medications, and consumer products. Furthermore, inhaled nanoparticles cleared from the respiratory tract can be also ingested [32]. The pH shift from the acidic stomach to the basic intestine “stresses” the nanoparticles and changes their solubility, ionic state, and surface properties, possibly increasing the health risks for humans [38].

Absorption of nanoparticles takes place at Peyer´s patches, secondary lymphoid organs that are cellular areas in the intestinal tissue belonging to the immune system. They are able to incorporate particles by phagocytosis, in series transcytosis can occur leading to nanoparticles entering the lymph system and being dispersed throughout the body by the bloodstream. The smaller the nano-size, the greater is the possibility that nanoparticles will deposit in different organs and have toxicological effects [75].

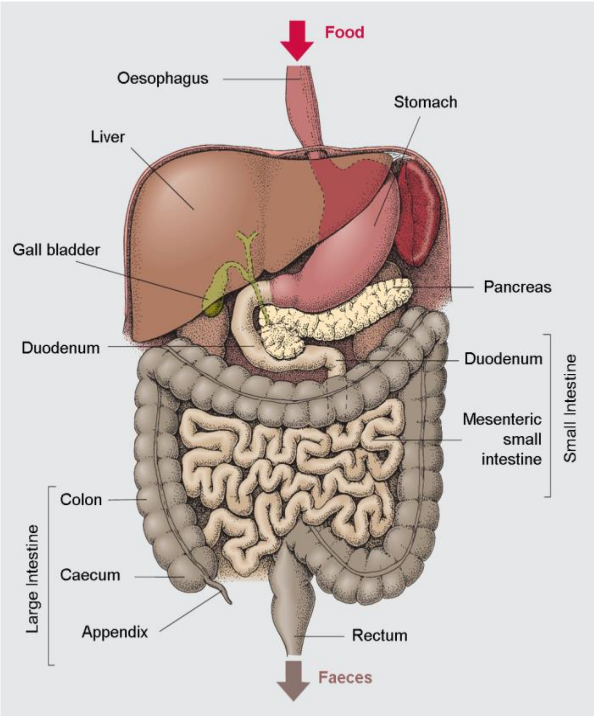

Fig. 6: Schematic representation of the gastrointestinal tract: Nanoparticle absorption can occur at Peyer´s patches. They are aggregations of lymphoid tissue usually found in the lowest portion of the small intestine in humans. Reprint and modification with permission from Huch / Jürgen: Mensch Körper Krankheit, 5.A. © Elsevier GmbH, Urban & Fischer Verlag Munich, Germany

A relatively new prospect for nanoparticles to enter the gastrointestinal tract is through the use of nano-toothpaste. Hypersensitive teeth pose a great problem in dentistry. Dentin, which is softer than dental enamel, is in direct contact with nerves. If it is dissected, pain ensues. Agents against this hypersensitivity are nano-capsules, consisting of phosphorite and apatite, a biomimetic ingredient for neomineralization. The apatite reacts with calcium in the saliva and phosphorite, and deposits on the dental surface. Further, deposited apatite attaches to the dentin and prohibits pain reactions [38, 53, 54]. However, long-term toxicological studies of these novel nanomaterials have not been published yet.

Another important application for nanotechnology is the food industry. A multiplicity of food industry is interested in designing food with new properties. According to one estimate, in 2010 the nano-food-industry will be worth €20 billion per year. Organic compounds are used as vehicles in order to solve, disperse or modify substances like vitamins or other food additives. This organic group is also used in food packaging to prevent the gas permeability and prolong storage life. In addition, inorganic nanoparticles like SiO_2 and TiO_2 are used as food additives in order to prolong the storage life and sightlines of chocolate. For example, Mars® has recently patented a new nano-layer-method [43]. For functional foods, many companies see a great potential in nanotechnology, for instance, in time-controlled release of ingredients to inhibit fat uptake [76]. However, long-term toxicological studies are not available and appropriate risk research is urgently advised. Discussions over chemical, analytical, and toxicological testing methods are still in their infancy as well as labeling of nano-food, in order to give the customer the option to decide and evaluate [77].

Nanomaterials: Distribution in the Human Body

Distribution of nanomaterials in the human body has been so far investigated in the range of drug design. The greatest amount of studies is conducted in the field of parenteral application of nanoparticles [78-83], which, along with orally ingested nanoparticles, are not further detailed in this report.

As a result of recycling processes, waste deposit, air, and groundwater, nanoparticles are distributed in the environment, yet until now it has not been possible to show whether nanoparticles ingested or inhaled from the environment are systemically absorbed on a larger magnitude and to calculate their long-term effects [35, 84].

Blood-Brain Barrier

In 1885 Paul Ehrlich demonstrated that acid vital pigments color the brain after injection into the cerebrospinal fluid (CSF) but not following intra-arterial injection. The real reason is the endothelium rather than the astroglial cells (Fig. 7).

The central nervous system shows a specific circular liquid flow: the adequate supply with blood and the production of CSF. The brain's interstitium differs from other interstitial spaces in the human body with regards to the small possibility for substance exchange due to the blood-brain barrier (BBB) [85].

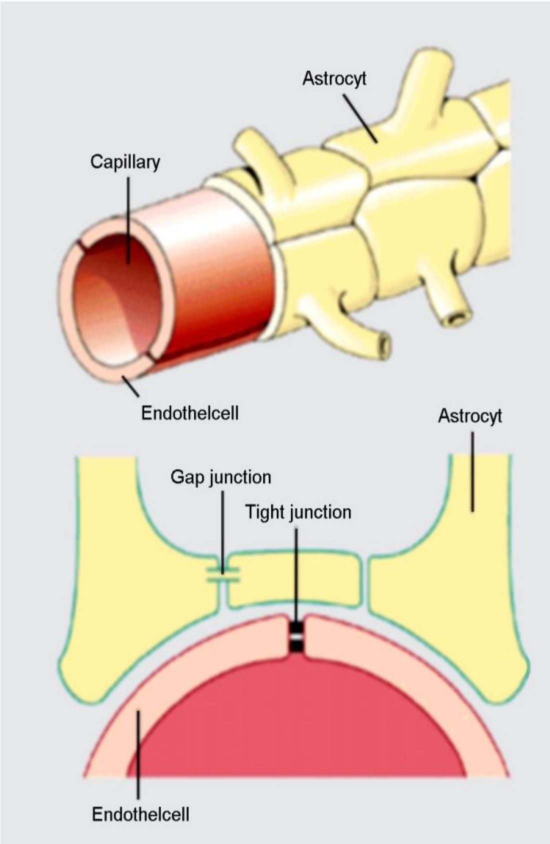

Fig. 7: The Blood-Brain Barrier: schematic modified representation of astroglial cells and the endothelium [86].

Brain tumors are life threatening diseases. A great problem in their medical treatment is the inability of many drugs to cross the BBB because the blood vessels of the cerebral endothelium are too compact. In addition, drugs transported by drug carrier systems can be immediately pumped out of the endothelium and the tumour infiltrates the healthy tissue like cobwebs. Current investigations show that following intravenous injection with brain-specific supra-molecular systems and nanoparticles it seems to be possible to transport these drugs across the BBB. This capability has been demonstrated for eight drugs from different therapeutic fields. An infiltrative therapy of tumors in healthy brain areas also seems to be possible.

Up to date, it has not been proved whether nanoparticles applied to the skin, inhaled or ingested can make their way to the brain. Also, all macrophages in the human body that are exposed to nanoparticles respond with oxidative stress.

Therefore, the one important question is to investigate the way by which nanoparticles enter the bloodstream, and is certainly the first prerequisite for translocating to the brain [87, 88].

In the context of this report, it is not possible to dwell on the medical aspects of drug targeting. Unfortunately, the number of toxicological data for drugs as well as for consumer products is poor. There is only one investigation, already mentioned earlier, which showed an ability to transport nanomolecules into the brain through an inhalational route, however, again toxicological data are not available [30].

RESEARCH PROGRAMS

EU-Research Programs

The European Commission is aware of the importance of safe nanotoxicology products and the key role of nanotoxicology. In the future, Europe should maintain leadership in the field of nanotechnology. Janez Potocnik, a member of the European Commission for Science and Research adduced this in the following way:

"Europe needs to invest in knowledge to maintain its competitive edge in the global economy. Nanotechnology is a key area where Europe is in the lead, and we must ensure that we stay there. Nanotechnology has enormous potential for European industry and for society in general, so a clear strategy and decisive action is needed for research in this area. At the same time, we must take into account any possible health, safety and environmental risks and address them as early as we can." [89]

In order to maintain leadership in the field of nanotechnology, the research and technological development is an essential element in the functioning of EU Member States and countries having applied for EU membership. Therefore the European Commission has built framework programs for EU activities concerning science research and innovation. The framework programs support collaboration with Europe and internationally, promote mobility and coordination and invest in mobilizing research to create favorable conditions for EU industry to turn research into useful products and services. They also include specific support for research on the impact of human health and the environment at the earliest possible stage and ensure that ethical principles are always respected and citizens' concerns and expectations are taken into account [90].

The 6th Framework program had a budget of €20 billion for the years 2002 – 2006, with a principle objective to implement common European research programs. Three basic principles signify this Framework program:

1. Focusing and Integrating European Research

2. Structuring the European Research Area
3. Strengthening the Foundations of the European Research Area

Table 3 gives an overview oft the three basic principles.

Concerning modern nanotechnologies in the 6th Framework program, four EU projects were funded and are further explained below: Nanosafe, Nanotox, Nanoderm, and Impart.

Nanosafe I

The most important concern of the NANOSAFE project group is to promote an open dialogue, structured research and development of the impact of nanotechnology on human health and environment in order to create a collection of nanomaterials-specific rules. The first program concluded in August 2004 and NANOSAFE II is now in progress.

Detailed results of NANOSAFE I were published in a study of the VDI (The Association of German Engineers, Düsseldorf, Germany) technology centre in their Future Technology Series [93]. The project included nine companies from the R&D and industrial sectors. Besides the VDI's international companies, medical laboratories, universities, and institutes from all over Europe were represented. The project analyzed the risks of nanomaterials posed by the production, application, and use of consumer and industry products. NANOSAFE also assessed aspects concerning the health of producers and consumers and discussed possible measures.

Today, many more nanoparticles still attain to environment over natural processes than industrial production. Yet the application of nanotechnology is on the rise and technology risk assessment is becoming increasingly important. The NANOSAFE partner suggest recommending the existing regulatory instruments and checking the principles if they are appropriate for nanomaterials or not. Due to the different types of nanoparticles available, each product and application should be individually controlled [93].

Nanosafe II

NANOSAFE II (2005-2009) is the continuation of NANOSAFE I and its main focus lies in the production, transport and safety research. It has a budget of €7 million and a total of 24 research institutes, companies, and start-up firms are involved in this project.

Nanotox

The NANOTOX project (2005–2007), with a budget greater than €8 million, is funded by the European Commission of Science and Research and coordinated by a private UK-based organization, Chalex Research. One of the world's main producers of nanotubes, Nanocyl, is a participant in the NANOTOX project, as well as the University of Manchester and the University of Helsinki, which are key partners. The global aim of the NANOTOX project is to provide investigative support for the elucidation of the toxicological impact of nanoparticles on human health and the environment. The project's specific objectives are the identification of nano-risks, the quantification of risk and exposure assessment, and risk

Table 3: Overview of the 6th European Framework Program [91, 92]

Basic Principles	Content
1 a) Focusing and Integrating European Research	Life sciences Information Nanotechnology and nanosciences, knowledge-based functional materials, new production processes and devices Aeronautics and space Food quality and safety Sustainable development, global changes and ecosystems Citizens and government in a knowledge-based society
1 b) Specific Activities Covering a Wider Field of Research	Research for policy report New and emerging science and technologies Specific activities Specific international co-opertaion activities
2) Structuring the European Research Area	Research and innovation Human resources and mobility Research infrastructures Science and society
3) Strengthening the Foundations of the European Research Area	Co-ordination of research activities Development of research/innovation policies

characterization [94, 95].

Nanoderm

NANODERM is another research project funded by the European Commission with a budget of approximately €2.5 million. It includes a partnership between four universities and three research organizations. The project deals with the effects and the penetration of nanomaterials into the skin [92, 96].

Impart

IMPART, a program aimed at improving the understanding of the impact of nanoparticles on human health and the environment, accompanies the NANOTOX project and focuses the attention on the harmonization between the standard of knowledge and health and environmental effects. In addition, a communication platform between local, national, and international initiatives should be arranged [92].

Table 4 presents a summary of the contents of the decribed projects of the 6th Framework Program for Research

Table 4: EU projects of the 6th European Framework Program

EU Project	Content	References
Nanosafe I	Commitments of nanomaterial specific formalities Material research Production risks Application risks Health risks for producer and consumer Preventive measurements and implementation regards	[92]
Nanosafe II	Spray-coated methods for nanomaterial Methods for characterizing health effects Safe production and safe handling	[92]
Nanotox	Physical and chemical properties of different types of nanoparticles and agglomerated nanocrystals Manufacturing and use Human health effects and side effects Animal toxicology Environmental impacts Mutagenicity/genotoxicity Metabolism/ pharmacogenetics Standards for safe use Safe laboratory methods	[92]
Nanoderm	Portals of entry and penetration of nanomaterial into the skin Classification into risk groups Health-effects Production and consumption information	[92]
Impart	Impact of nanoparticles on human health Impact of nanoparticles on the environment Communication platform	[92]

The Future of the European Framework

The 7th European Framework Program for Research and Technological Development will last for seven years, from 2007 till 2013. It is divided into specific sections and has a budget of €54 Billion, an increase of about 60% in comparison to the 6th Framework program. The objectives are to strengthen the scientific and technological base of European industry and to encourage its international competitiveness.

The 7th European Framework Program is constituted into five principles:

1. cooperation
2. ideas
3. people
4. capacities
5. nuclear research

Table 5 gives a short summary about the structure and the targets [97, 98].

National Research Programs in Austria

At the national level, nanotechnology has been supported by various organizations for many years. The basic research is led by the Austrian Science Fund (FWF), programs with industrial partner are supported Austrian Research Promotion Agency (FFG). Since 2004 and under the guidance of the governance of transport, innovation and technology the FFG has been instructed, to create a special nanotechnology program, the Austrian nano-initiative, having the following goals:

- Research and Technology, and Development of Project Cluster
- Network and Confidence Building
- Training and Education Measures
- Accompanying Measures

Within this initiative, it is assumed that risk-assessment for nanotechnology will also be conducted in Austria and will have an important impact in the future [98].

SUMMARY

The main aim of the presented study is to answer the question whether nanoparticles, following oral, nasal or dermal penetration, remain in the body and do they have toxic consequences. Basically, nanoparticles are excreted as any other foreign substances. However, when it comes to synthetic nanomaterials, the body may not identify the nanoparticles or nanotubes as foreign material. Therefore, they could settle in different organs, for example, liver, spleen, bone marrow, or lungs and depending on the material's composition, lead to various processes in the organs [99]. Biologically degradable nanoparticles, which were ingested, disintegrate and their metabolites are excreted through the intestine. However, non-biologically degradable nanoparticles pose a problem.

Table 5: Overview of the 7th European Framework Program [92, 99]

Basic Principles	Content
1) Cooperation	Health Food, agriculture, biotechnology Information and communication technologies Nanoscience, Nanotechnology, materials, and production techniques Energy Environment Transport Social science, economics, and humanities Safety research Space Aerospace
2) Ideas	Support of frontier research including engineering, socio.economic sciences and humanities
3) People	Initial training of researchers Industry-academia partnerships Co-funding of regional, national and international mobility programs Intr-european fellowship International dimension Awards
4) Capacities	Research infrastrucutures Regions of knowledge Research potential Science in society Specific activities
5) Nuclear Research	Fusion energy research Nuclear fission and radiation protection Nuclear waste management Safety Security

Investigations have been conducted, yet the results are not conclusive concerning long-term toxicity.

The nasal absorption of nanoparticles has not been conducted yet. Most of the published studies deal with the toxicological risks following non wanted inhalation into the lungs. Potential risks for the nasal mucosa and in series for the neuronal connection to the brain have to be taken into consideration.

Many studies have been conducted involving the inhaled route. While some were concerned with correct dosing, others focused on the nanoparticles' mechanism of deposition and the effects in the lung. Long term studies however, are still lacking.

In March 2006 "Magic Nano Bath and Toilet Cleaner" and "Magic Nano Glass and Ceramic Sealing" were introduced in Europe; two spray products with soil resistant and water repellent effects. Shortly after the sprays were introduced, 74 intoxication cases contacted the intoxication information centre with symptoms like dyspnea and cough after using these products. In six of the 74 cases lung edema was diagnosed. The sale was immediately halted. Investigations were made by the Federal Institute for Risk Assessment for both products but nanoparticles could not be found. However, it is still suspected that an anti-corrosive component could be responsible for this accident [81, 89]. Furthermore, the German Federal Ministry observed that both products (as pump-sprays) have been sold for four years without any declaration [100].

The dermal applications of nanoparticles as a cream or ointment has been investigated but there is still very little data describing the uptake. Also, there is a need of long-term studies because of the rapidly increasing number of products in the cosmetics field, given the ease of the authorization procedure. Sunscreens for babies and children with TiO_2 or ZnO nanoparticles, acting as a mineral UV filter, are increasingly applied even though the skin of children is more sensitive. The Food and Drug Administration (FDA) classifies TiO_2 nanoparticles as a variation of the bulk material, thus long-term toxicological studies are not necessary before a product enters the market. Furthermore, the "Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers" also advances the view of the FDA [101]. The results of the NANODERM project, showed that TiO_2 nanoparticles remain in the epidermis and only a very small amount enters the dermis through the hair-follicles, significant for nanoparticles with a size > 20 nm and for healthy skin. Investigations on sunburned or injured skin have not been published yet [70].

In contrast to the dermal absorption, nanomaterials can be ingested into the gastrointestinal tract in two ways – when they are cleared from the respiratory tract or directly, if they are contained in food, water, medications and consumer products and. Because of the pH shift nanoparticles can be stressed, change their solubility and surface properties. However, very little is known about their potential of increasing the health risks for humans and long term studies are missing.

Nanotechnology is associated with high expectations. Products with completely new properties for applications in medicine, science, industry and techniques are designed. The question about risks for health and environment should not be disregarded. The greatest potential for exposure, over the next few years, will be in the workplace, in industry, and university. This fact is addressed by insurance concerns, like the Swiss Reinsurance Company Zurich, Switzerland. Producers of nanomaterial products must take into account the differences in the toxic potential between larger and nano-sized particles. Measures of precaution must be developed to control airborne concentrations of nanoparticles in industry in order to avoid a second "asbestos thematic" [12]. Legal employment protection, for those subjected to nanomaterials are lacking in the EU. The use of nanotechnological products will dramatically increase over the next decade - not only for medical applications but also for food, cosmetics, textiles, and other consumer products.

Another important point in risk management is the impact of nanotechnology on the environment. Prof. H. F. Krug from the Empa, Dept. Materials-Biology Interactions, St. Gallen, Switzerland suggests four points that need to be taken into consideration:

1. investigations of the mechanisms of actions at the cellular and molecular levels
2. development of systems
3. involving of ecological consequences
4. assessment of possible detrimental effects on the whole life cycle and a better database [84].

Scientists at the EMPA (Institute of Materials Science and Technology, St.Gallen, Switzerland) in cooperation with researchers at the Eidgenössische Technische Hochschule Zurich, Switzerland, (ETH Zurich) test systems in order to define risk assessment of nanotoxicity without conducting animal experiments. A human mesothelioma and a rodent fibroblast cell line were used to investigate seven industrially important nanoparticles. As an indicator of the cell's metabolic activity, cell proliferation and appearance were monitored. The response was compared to the effects of non-toxic amorphous silica and toxic crocidolite asbestos. The results showed that solubility strongly influences the cytotoxic response of all seven tested oxide nanoparticles. Zinc oxide and iron oxide, two soluble oxide nanoparticles, demonstrated cytotoxic effects. Insoluble nanoparticles, like titanium oxide, a redox active, Ceria oxide and zirconium oxide, two redox inert, also affected the cell's metabolism. Furthermore, it could be shown that relatively simple cell culture conversion and DNA content tests can be useful assays to make comparative statements about different nanoparticles. Furthermore, human mesothelioma cells are more sensitive than fibroblasts [102].

In summary, an initial evaluation of health, safety and environmental risk must be done and risk assessment needs to be taken into consideration in research studies.

CONCLUSIONS

Nanotechnology research is growing rapidly worldwide, and with variations of the bulk substance, the materials' reactivity changes allowing nanomaterials to enter the human body through inhalation, ingestion, skin absorption or injection.

The benefits of nanomedicine are already known and wildly publicized, ensuring that the introduction of nanomedical products into the market will be well supervised. In comparison to other medical products, nanomaterial used in the average consumer goods is "just" a variation of the bulk material; therefore, long term toxicological studies must not be conducted before a consumer product enters the market. However, regulations, nanomaterials-specific data on toxicity must be collected before a product enters the market. Guidelines should be developed for risk assessment and a free and an open archive for scientific and technical nanotechnology data should be complemented.

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