

Nanomaterials and Their Effects on Health

Nanomalzemeler ve Sağlık Etkileri

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ABSTRACT

Nanotechnology, which includes many potential applications, is described as the technology of the future and the industrial revolution of the 21st century. The effect of nanotechnology is particularly evident in nanomaterials (NMs) used for chemicals, pharmaceuticals, and personal care products. Properties such as nanoscale size, large surface area, and surface activity make NMs attractive for many applications. It is estimated that more than 1600 nanoscale products are on the market today and that by 2020, more than six million employees will be exposed to engineered nanoparticles (NPs).

Due to the observed changes in the physical, chemical, and toxicological properties of the material in parallel with the decreasing particle size, it is predicted that NPs may cause adverse effects on biological systems. However, due to the relative novelty of nanotechnology, there is a lack of knowledge about the ways humans are exposed to NPs and the possible adverse health effects of NPs. Knowledge of the effects of long-term exposure to engineered NPs on human health is based on *in vitro* studies, *in vivo* animal studies, and a limited number of human exposure studies. In our country, there are no studies in this field. A better understanding of the health effects of NPs, which is expected to have increased production in our country soon, is a scientific necessity to be dealt with for the safe use of NMs. Therefore, it is aimed to evaluate the effects of NPs on human health in the light of current information and to draw attention to the dangers that may develop.

Keywords: Nanomaterials, nanotechnology, nanoparticle, health effects

ÖZ

Pek çok potansiyel uygulama içeren nanoteknoloji, geleceğin teknolojisi ve 21. yüzyılın endüstriyel devrimi olarak nitelenmektedir. Nanoteknolojinin etkisi özellikle kimyasallar, ilaç ve kişisel bakım ürünleri için kullanılan nanomalzemelerde görülmektedir. Nano-ölçekli boyutu, geniş yüzey alanı ve yüzey aktivitesi gibi özellikler nanomalzemeleri çok fazla uygulama için ilgi çekici kılar. Günümüzde 1600'den fazla nanoboyutlu ürünün piyasada bulunduğu ve 2020 yılına kadar altı milyondan fazla çalışanın mühendislik ürünü nanopartiküllere maruz kalacağı tahmin edilmektedir.

Küçülen parçacık boyutuyla paralel olarak malzemenin fiziksel, kimyasal ve toksikolojik özelliklerinde gözlenen değişiklikler nedeniyle nanopartiküllerin, biyolojik sistemler üzerine olumsuz etkilere neden olabileceği öngörülmektedir. Bununla birlikte, nanoteknolojinin görece yeniliği nedeniyle, insanların nanopartiküllere maruziyet yolları ve nanopartiküllerin olası olumsuz sağlık etkileri hakkında bilgi eksikliği vardır. Mühendislik ürünü nanopartiküllere uzun süreli maruziyetin, insan sağlığı üzerine etkileri hakkındaki bilgi birikimi, *in vitro* çalışmalar, *in vivo* hayvan çalışmaları ve sınırlı sayıdaki insan maruziyet çalışmalarına dayanmaktadır. Ülkemizde ise bu alanda yapılmış çalışma bulunmamaktadır. Yakın zamanda ülkemizde de üretim artışı beklenen nanopartiküllerin sağlık etkilerinin daha iyi anlaşılması, nanomalzemelerin güvenli kullanımı için, ele alınması gereken bilimsel bir zorunluluktur. Bu nedenle makalede güncel bilgiler ışığında nanopartiküllerin insan sağlığı üzerine etkilerinin değerlendirilmesi ve böylece gelişebilecek tehlikelere dikkat çekmek amaçlanmıştır.

Anahtar Kelimeler: Nanomalzeme, nanoteknoloji, nanopartikül, sağlık etkileri

Introduction

Nanotechnology, a rapidly growing science that integrates engineering with biology, chemistry, and physics, is regarded by scientists as the industrial revolution of the 21st century (1). When the dimensions of solid

material are reduced to nanometer (nm) dimensions, their physical and chemical properties change. In order to take advantage of these features, we still lack serious information about the health effects of nanomaterials (NMs), which have been increasing in production in recent years (2).



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NMs are potentially useful nanoscale materials with unique properties. The International Organization for Standardization defines the term “NM” as “material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale”. One nm is defined as the one billionth of a meter, and “nanoscale” is used to express length range approximately from 1 nm to 100 nm (3).

Properties such as nanoscale size, large surface area, and surface activity make NMs interesting for many applications (4). In a study conducted in 2011, the number of NMs produced as a consumer product by 24 countries worldwide was found to increase from 212 to 1317 (5). It is estimated that more than 1600 nanoscale products are on the market today, and more than 6 million employees will be exposed to engineered nanoparticles (NP) by 2020 (6).

NMs are used in many areas such as computer chip technology, automotive catalytic converters, air and space vehicles, food, cosmetics (lipstick, sunscreens, anti-aging creams), dental prostheses and orthopedic implants (7,8). There are more than 800 consumer products with different NM types. It is thought that a person consumes an average of 1012 NPs per day in a standard diet due to food additives (7).

In addition to consumer products, nanoscale molecules are also used in the drug transport system as nanotransporters. Nanotransporter systems have been developed to provide advantages such as reducing drug degradation and loss, preventing possible side effects, increasing drug biocompatibility, and being able to transport the drug in various regions in a controlled manner. These drug transport systems are divided into various classes, such as micelles, dendrimers, liposomes, NPs, and carbon nanotubes (CNT) (9,10). Each has advantages and disadvantages. In the future, it is thought that the release and effect of drugs will happen via nanotransporters with “compliance and time” adjustment through controlling toxicity and regional effects by clinicians and researchers (11). However, since most clinical research reports for nanomedicine products focus mainly on the therapeutic efficacy of drugs, human biosecurity information is limited. In order to evaluate the human biosafety of nanomedicine products in clinical studies, it has been reported that a standardized test battery should be developed, including all indices of blood chemistry, carcinogenic, teratogenic, mutagenic toxicities and immune, nervous and reproductive systems (12).

NMs are grouped according to their size, morphology, production methods, and compositions. Nanostructures are divided into three according to size: a) One-dimensional nanostructures, commonly referred to as thin films, are technologies used in computer chips, anti-reflective coatings and sunglasses, b) two-dimensional nanostructures are nanowires and CNT used in separation and filtration technologies, c) three-dimensional nanostructures include perforated structures, colloids and quantum structures in atomic structure (13). NMs can be a pipe, rod, wire, or sphere according to their morphological structures. Depending on their source, they can be categorized, as engineered NPs and incidental NPs. Engineered NPs are particles produced to use nanometer-specific size-dependent properties (e.g., conductivity, spectral properties, biological distribution). Incidental NPs are defined as NPs that are either formed from anthropogenic sources (e.g., cigarette

smoke, diesel fuel exhausts, industrial by-products) or naturally (e.g., marine spray, volcanic ash). Engineered NMs, including NP and nanofibers, are divided into four classes according to compounds: a) carbon-based materials (CNT, graphene, fullerene), b) metal-based materials (quantum dots, nanosilver, nanogold, titanium dioxide), c) dendrimers (nanoscale polymers) and d) composites (7).

Clinical and Research Effects

Nanoparticle Exposure

In addition to occupational exposure to NPs, direct human exposure with medical applications, and air pollution in the environment is a significant concern (14). NPs are taken into the human body through various exposure routes such as respiration, skin, and gastrointestinal tract during the production and consumption processes (15). The size of the nanostructures is very small, and their mass is relatively light. Therefore, especially in the working environment, the main entry route for NP is the respiratory system (15,16). The size of the airborne particles reaching the airways affects the depth of the airways through which the particles can enter and their target organs (2). The primary deposition site of the NP, which is several tens of nanometers in size, is the alveolar area. From the NP reaching the alveoli, those within a range of several nm may reach the systemic circulation through the alveolar wall (17). Thus, they are translocated into secondary organs such as the liver, spleen, and kidney (18). It is estimated that the translocation of the inhaled NP into the circulation and secondary organs is less than 1% of the total mass-based amount. However, this rate is based on estimates from animal studies, and there is a lack of information on the biokinetics of inhaled NP and its long-term effects on humans (19).

Dermal exposure may occur during the application of topical creams and other drug treatments or accidental exposure (20). However, there are controversial data about the dermal absorption of NP. In contrast to studies reporting that NP cannot penetrate the dermis, Oberdörster et al. (21) demonstrated the penetration of various NPs in the dermis and translocation into the systemic circulation through the lymphatic system and regional lymph.

NPs may also enter the body indirectly after mucociliary clearance in the nasal region or directly through the gastrointestinal tract as a result of food, water, cosmetics, and drug consumption (20,21). Without dosimetry and particle kinetics data, it is currently difficult to accurately assess the potential toxicity of foodborne NMs. Besides the direct effects of foodborne NMs, chronic NP exposure is thought to play a role in the development of inflammatory diseases with the potential to disrupt the normal microbiota balance in the gastrointestinal tract (22).

Limited to engineered materials, injections, and implants are also possible routes of exposure. Intravenous and oral administration has a faster systemic effect compared to other routes (23). Since these particles can easily pass into the circulatory system, they can reach the lymph and nervous system and reach many organs, including the brain (24). Also, injected NPs are rapidly absorbed by the liver and kidneys from the circulatory system (18).

The Effects of Nanoparticles on Health

The health effects of NPs may vary depending on the number of physicochemical properties such as size, shape, surface properties, composition, solubility, aggregation/agglomeration, and the presence of mutagens and transition metals in the particles (25). Many engineered NPs have increased surface reactivity and, therefore, may cause local damage by inducing inflammation at the site of accumulation and the formation of reactive oxygen species (ROS) (26,27). NP-induced ROS plays a crucial role in cell and tissue toxicity (28). Overproduction of ROS can trigger oxidative stress, which causes the cells to fail normal physiological redox reactions; thus, it leads to DNA damage, deterioration in cell signaling, changes in cell motility, cytotoxicity, apoptosis and the onset of cancer (29).

ROS are associated with different stages of carcinogenesis, including epigenetic changes, DNA damage, and protein and lipid changes (29). Metal-based NPs, especially silver, gold, and titanium, are essential for ROS production and genetic damage (30). In a recent study, workers with occupational exposure to metal oxide NMs in 14 factories producing and using NMs in Taiwan were evaluated for the first time for epigenetic alteration (methylation) and oxidative DNA damage. In this study, oxidative stress biomarkers and DNA methylation of 87 employees with exposure to metal oxide NMs (titanium dioxide, silicon dioxide, and indium dioxide) and 43 employees with no exposure were compared, and exposure to metal oxide NMs has been shown to cause methylation, oxidative damage to DNA, and lipid peroxidation (31).

It is vital to assess genotoxicity to protect employees from the potentially harmful effects of engineered NPs. Since many commonly used genotoxicity tests are adapted for soluble chemicals rather than particulates, genotoxicity test results for NPs are skeptical (4). However, some *in vitro* and *in vivo* studies have provided useful information on the relationship between NP exposure and genotoxicity in the working environment (32). In the study of Lindberg et al. (33), it was shown that genotoxic changes occurred in pulmonary epithelial cell culture with low doses of carbon CNT and graphite nanofiber exposure. Subsequently, in Lindberg et al. (33) study, human lymphocyte cells were exposed to single-walled CNT (SWCNT), and multi-walled CNT (MWCNT) in low and moderate doses (6.25-300/g/mL) and this finding was confirmed by demonstrating chromosomal abnormalities (33). The point that should be considered in these studies is that genotoxic effects have been observed at the exposure levels expected in occupational environments (2).

From the experimental results, a study was conducted to evaluate potential genotoxic effects of NMs in humans and found significant changes in the messenger RNA and non-coding expression profiles in the sera of workers (eight workers) exposed to MWCNT for more than six months compared to those without exposure (seven workers). Also, described pathways and signaling networks have revealed the potential of MWCNT to produce carcinogenic results in humans as well as pulmonary and cardiovascular effects, similar to rodents previously exposed to MWCNT (34).

As the size of the particles reaching the airways becomes smaller, the depth of the airways through which the particles can enter increases, and thus their effects on the target organs change. In studies evaluating the

relationship between particle size and lung inflammation and toxicity, engineered NPs and coarse particles were compared, and a higher rate of lung inflammation and toxicity response to NPs was observed (35,36).

NPs are thought to cause pathological changes in the lung regardless of dose. In two independent studies, mice exposed to SWCNT at doses of 3.3-16.6 mg/kg and 10-40 ug/mouse have developed a strong acute inflammatory response, with the development of pulmonary fibrosis leading to impaired pulmonary function (37,38).

Although we have limited data on engineered NPs, many epidemiological studies have shown a direct coherence between the increased amounts of incidental NP produced in indoor air and the increased adverse health effects associated with cardiovascular disease. There is a strong link that supports the relationship between inflammation and coronary heart disease because inflammation has been proven to be directly associated with atherosclerosis (39). Data from human studies support the link between PM air pollution and the development of cardiac responses leading to atherosclerosis (40). In the review of epidemiological studies, Delfino et al. (41) have clearly demonstrated pathophysiological changes that induce cardiovascular diseases by exposure to ultra-fine particles. In a recent animal study, titanium NPs have been shown to affect ventricular cardiomyocytes besides indirect inflammatory effects directly. In rodents exposed to intratracheal titanium dioxide NPs, shortened repolarization time, increased cardiac conduction and excitability rate, and ventricular arrhythmia were observed (42).

Although there are few epidemiological studies showing the direct effect of engineered NPs on human health in the literature, the known health effects of NMs in the guideline published by WHO in 2017 including all the studies conducted were divided into nine categories: Acute toxicity, skin corrosion/irritation, eye damage/irritation, respiratory and skin sensitization, genotoxicity, carcinogenicity, reproductive system toxicity, specific target organ toxicity following single exposure and specific target organ toxicity following repeated exposure. In the guideline (19), the effects of 11 NMs on human health were for summarized as follows:

Fullerene: There is evidence that it does not cause acute toxicity, skin, eye, respiratory damage, genotoxicity, and specific target organ toxicity after repeated exposure, but data are lacking for other hazard categories.

SWCNT: There is evidence of genotoxicity and specific target organ toxicity after repeated exposure (low level of evidence). There is evidence that it does not cause acute toxicity, eye and skin damage, and respiratory/skin sensitization. There is no data showing that it causes reproductive system toxicity and specific target organ toxicity after a single exposure. It has been classed as group 3 (those that cannot be classified as carcinogenic in humans) by the International Agency for Research on Cancer (IARC).

MWCNT: There is evidence of eye damage (strong grade of evidence), genotoxicity (strong grade of evidence), carcinogenicity (moderate grade of evidence), and specific target organ toxicity following repeated exposure (moderate grade of evidence). There is evidence that it does not cause acute toxicity, skin damage, respiratory/skin sensitization, and reproductive system toxicity. There is no evidence of specific target organ toxicity following a single exposure. MWCNT-7 has been classed as

group 2B (possibly carcinogenic in humans) by IARC and other MWCNTs as group 3 (those that cannot be classified as carcinogenic in humans).

Silver NPs: There is evidence of respiratory/skin sensitization (moderate grade of evidence), and specific target organ toxicity following repeated inhalation and oral exposure (strong grade of evidence). There is evidence that they do not cause acute toxicity, eye damage, and genotoxicity. There is no evidence of carcinogenicity and specific target organ toxicity following a single exposure.

Gold NPs: There is evidence of specific target organ toxicity following repeated inhalation exposure (strong grade of evidence). There is no data for other classes.

Silicon dioxide: There is evidence of specific target organ toxicity following repeated inhalation exposure (strong grade of evidence). There is evidence that it does not cause acute toxicity, eye and skin damage, respiratory and skin sensitization, genotoxicity, and reproductive system toxicity. There is no data for carcinogenicity and specific target organ toxicity following a single exposure.

Titanium dioxide: There is evidence of reproductive system toxicity (moderate grade of evidence) and specific target organ toxicity (strong grade of evidence) following repeated inhalation exposure. There is evidence that it does not cause acute toxicity, skin and eye damage, respiratory and skin sensitization, and genotoxicity. There is no data for specific target organ toxicity following a single exposure. It has been classed as group 2B (possibly carcinogenic in humans) by IARC.

Cerium dioxide: There is evidence of specific target organ toxicity following repeated inhalation exposure (moderate grade of evidence). There is evidence that it does not cause acute toxicity. There is no data available for other hazard classes.

Dendrimers and nanoclays: There is no data on hazard classes.

Zinc oxide: There is evidence of specific target organ toxicity following repeated inhalation exposure (moderate grade of evidence). There is evidence that they do not cause acute toxicity, skin and eye damage, genotoxicity, and reproductive system toxicity. There is no data on respiratory/skin sensitization, carcinogenicity, and specific target organ toxicity following a single exposure.

As a result, it is emphasized in the guideline that prudence should be taken against engineered NPs that we do not yet know the health risks and that the proactive approach should minimize the exposure of workers (19).

Conclusion

Features such as nanoscale size, large surface area, and surface activity make NMs appealing for many applications. Therefore, nanoscale materials are increasingly used in many areas of daily life, such as industry, science, pharmacy, medicine, electronics, communications, and consumer products. Although it is predicted that NPs may cause adverse effects on biological systems due to the observed changes in the physical, chemical and toxicological properties of the material in parallel with the decreasing particle size, unfortunately, there is still a lack of data about the ways people are exposed to NP and the possible

negative health effects of NPs. Toxicological assessment of these new materials is a scientific necessity that needs to be addressed in order to recognize risks, avoid potential hazards, and safe use of NPs. Although humans have been exposed to unwanted NPs for the long-term due to combustion processes, the recent increase in engineered production of NMs requires further investigation into potential toxicity and adverse health effects after exposure. Since the potential health effects of newly engineered NMs have not been sufficiently tested, a prudent approach should be adopted until they reach reliable results.

Ethics

Peer-review: Externally peer-reviewed.

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