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REVIEW

Impact of nanomaterials on human health: a review

Eylem Asmatulu[1] · Mohammad Nahid Andalib[2] · Balakrishnan Subeshan[1] · Farhana Abedin[3]

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Abstract
Nanomaterials are now widely used in various industries such as automotive, biomedical, cosmetics, defense, energy, and electronics, due to their unique properties. However, this ubiquitous presence of nanomaterials in the environment is inducing possible major issues of toxicity for humans. Indeed, nanomaterials can elicit toxicity in human cells. Here, we review nanomaterial exposure to humans, with focus on impact on human cells and animal models. We discuss mainly nanomaterials made of silver, gold, silica, quantum dots, iron oxides, zinc oxide, and titanium dioxide. There is evidence that nanomaterials accumulate in the heart, liver, spleen, kidney, and brain by including ingestion, dermal penetration, inhalation, and intravenous.

Keywords Nanomaterials · Human health · Human exposure · Toxicity

Introduction

Over the twentieth and twenty-first centuries, the field of nanotechnology has expanded, which in turn has accelerated the rise in number of novel nanomaterials being industrialized. The establishment of these new nanomaterials is likely due to their exceptional, size-reliant physical and chemical properties. Nanotechnology is undoubtedly performing a crucial part in modernization and the economy for many industries. Nanomaterials are featured according to their explicit attributes such as surface charge, surface area, surface coating, particle morphology, and degree of agglomeration (Jeevanandam et al. 2018; Subhan et al. 2021). Nevertheless, it has been shown that those modifications within the essential characteristics of the bulk material form the base in place of a upper size limit. Nanomaterials can be synthetically manufactured for commercial purposes, potentially be an unintended by-product, or, instead, materialize naturally. Nanomaterials exist in natural surroundings that then discover a path to enter the human body or impact human health as they make contact with humans through direct or indirect methods (Malakar et al. 2021).

The latest research has concentrated on improving and increasing the viability of nanotechnology. As a result, improvement in the utilization of nanomaterials has increased exponentially, intensifying their existence in various natural resources, water, air, and soil (Saeedi et al. 2019). The increased usage of nanomaterials is reflected in the significance of exploring their possible impact on human health over the past decade. Submicron-scale particles are ultrafine particles that are typically freed within the surrounding area through fossil fuel combustion or industrialized emissions, although engineered nanomaterials can be produced as the result of controlled practices (Li et al. 2016). This category of nanomaterials could have detrimental impacts on humans, including inflammation, allergy, asthma, genetic mutation, and signaling pathway intervention. Furthermore, they could harmfully damage cardiovascular and respiratory systems (Li et al. 2016). Engineered nanomaterials have turned out to be fascinating in numerous applications because of the special abilities imparted by their nanoscale size. Both their commercial manufacture and need are on the upsurge (Khan et al. 2019). Along with the intensified need for engineered nanomaterials in consumer goods, concerns about their impact on human health and surroundings have been amplified. Data on the number of engineered nanomaterials and

✉ Farhana Abedin
fabedin@cpp.edu

[1] Department of Mechanical Engineering, Wichita State University, 1845 Fairmount Street, Wichita, KS 67260, USA

[2] Department of Mechanical and Materials Engineering, University of Nebraska-Lincoln, Lincoln, USA

[3] Department of Electromechanical Engineering Technology, California State Polytechnic University, Pomona, 3801 West Temple Avenue, Pomona, CA 91768, USA

their allocation in several products is non-existent (Piccinno et al. 2012). An integral part of the risk assessment of engineered nanomaterials involves their quantity, distribution, product life cycle, and product outcomes (Piccinno et al. 2012). Since nanomaterials can be toxic, risk evaluations to humans and their surroundings are highly significant as their need continues to rise.

This study discusses not only the integration of research on the role of engineered nanomaterials and their potential impact on human health, but also current knowledge gaps. Most investigations corresponding to the toxicity of engineered nanomaterials have been driven by in vitro or in vivo studies utilizing animal models. Consequently, most of the exploration on toxicity can obliquely pertain to humans (Savage et al. 2019). The main subject in this paper is the impact of titanium dioxide, carbonaceous, silver, and silica nanoparticles on different cell lines and animal models. This review summarizes the various categories of engineered nanomaterials. The literature has been summarized, based primarily on potential human exposure and human health impacts, reflecting on exposure routes including air, water, and food, and regarding agronomic crops that accrue nanomaterials from the soil. The influence of nanomaterials on human health will be carefully evaluated. The predominant knowledge gaps will be discussed relative to prospective options for the future.

This article is an abridged version of the chapter by Asmatulu et al. that will be published in the book series Environmental Chemistry for a Sustainable World (Abedin et al. 2021).

Production of engineered nanomaterials

Synthetic nanomaterials are produced as both intended and unintended nanoscale materials through human intervention. Nevertheless, the annual transition of synthetic nanomaterial into the environment is considerably much lower than that of natural nanomaterial and is expected to release about 10.3 megatons per year into the atmosphere (Shukla and Iravani 2017). Although synthetic nanomaterials are tiny in volume, in contrast to natural nanomaterials, they are still a hazard to their surroundings and are referred to as contaminants. Synthetic nanomaterials are generally grouped as incidental nanomaterials along with engineered nanomaterials (Barhoum et al. 2022). The latest report summarizes synthetic nanomaterials that could be freed into urban surroundings from different sources (Amenta et al. 2015).

Nanomaterials manufactured for marketable intent are designated as engineered nanomaterials. They are used extensively and encompass telecommunications, information technology, agrochemicals, personal care products, and energy fields (Aslani et al. 2014; Donia and Carbone 2019; Resnik 2019). Furthermore, their need is growing every day, along with further engineered nanomaterials are making their path toward numerous water sources. Engineered nanomaterials are utilized in practically every area of technology, from quantum computing to agriculture. They can be comprehensively categorized depending on their morphology—0D (quantum dots), 1D (nanorods), 2D (graphene), or 3D (fullerene)—as well as their composition, including carbon and metallic established nanomaterials (Paramasivam et al. 2021). The applications and characteristics of different engineered nanomaterials are summarized in Table 1.

Morphology-based engineered nanomaterials

The categorization of nanomaterials is simply dependent on the mobility of an electron. Non-porous palladium nanoparticles are a representation of 0D, for 2D graphene nanosheets, silver nanorods along with polyethylene oxide nanofibers represent for 1D as well as tungsten oxide nanowires and zinc oxide nanowires denote for 3D nanomaterials, correspondingly. The electron is usually caught in dimensionless space in 0D nanomaterials, encompasses a unidirectional space for 1D nanomaterials, and encompasses bi-directional and multi-directional space in 2D and 3D nanomaterials, respectively (Korotcenkov 2020). 0D along with 1D nanomaterials are prevalent and have been manufactured in massive quantities for commercial purposes. Two-dimensional nanomaterials represent a comparatively novel and fascinating high member among various nanomaterials (Zhang 2015). Graphene is a familiar instance of 2D nanomaterials. Two-dimensional nanomaterials, along with their nanocomposites, have presented outstanding chemical, physical, electronic, and optical attributes, which have helped their advanced usage in energy, bioimaging, catalysis, anti-bacterial, drug delivery, sensing, and therapy applications (Cai and Yang 2020). Three-dimensional printing is a manufacturing technology established on an automated computerized model that builds a 3D structure using a layer-by-layer discrete-cumulative process. Three-dimensional macrostructures have been created by self-assembly of 2D graphene oxide as well as 1D carbon nanotubes, and research has identified that 3D microstructures reveal more advanced adsorption properties than emerging and conventional contaminants (Asmatulu et al. 2018, 2020).

Composition-based engineered nanomaterials

Engineering nanomaterials, grouped by their composition, may be produced and originate from carbon bases such as carbon nanotubes, organic nanomaterials such as lipid or polymer nanomaterials, along with metals similar to zerovalent metalloids, for instance cadmium sulfide nanorods (Luo et al. 2021). Gold and gold-based nanomaterials

Table 1 Applications and characteristics of engineered nanomaterials

Nanomaterial	Size	Shape	Application	Characteristics	References
Carbon-based MWCNTs	lower than 200 nm	Cylinder	Solar cells, transistors, energy storage, composite fabrication	High tensile strength, high electrical conductivity, high elasticity	Yuan et al. (2017)
Carbon-based SWCNTs	lower than 10 nm	Cylinder	Sensor manufacturing, drug delivery, biomedical applications	High electrical conductivity, high thermal conductivity	Yuan et al. (2017)
Carbon-based fullerene	~ 1 nm	Sphere	Cosmetics, electronics, drug delivery, energy applications	Anti-oxidants	Hao et al. (2018)
Carbon black	10–500 nm	Sphere	Electric conductors, rubber by-products, coatings, leather products	Electrical conductivity, thermal conductivity, UV resistance, anti-oxidants, reinforced effect	Stark et al. (2015)
Graphene nanoparticles	1–100 nm	Hexagonal ring	Sensor manufacturing, fuel cells, supercapacitors, transistors, biomedical applications	Electrical conductivity, thermal conductivity, large surface area, high elasticity, chemical inertness	Li et al. (2021)
TiO_2 nanoparticles	5–200 nm	Nanocube, nanorod, nanosphere	Cosmetics, inks, drug delivery, pharmaceuticals, food products, plastics, toothpaste	High stability, anti-corrosion, photocatalyst, high refractive index	Garner et al. (2018)
Ag nanoparticles	25–35 nm	Flower-shaped, hexagon, octagon, triangle, nanosphere	Cosmetics, implants and catheters, water purifiers, apparel, food products	Anti-microbial, anti-viral, anti-bacterial	Yan and Chen (2019)
Au nanoparticles	5–15 nm	Nanocage, nanorod, nanoshell, nanosphere	Drug delivery, biosensing, theragnostic application, bioimaging	Flexible for modification, optical activity	Wang et al. (2018)
Silica nanoparticles	4–30 nm	Nanocube, nanorod, nanosphere	Fuel cells, catalysts, energy storage, drug delivery, medical imaging	Biodegradable, easily modified surface, large surface area, large pore volume	Bastos et al. (2017)
Quantum dots modified CdS	10–20 nm	Dot	Solar cells, quantum computing, cancer therapy, drug delivery	High photostability, broad absorption, narrow emission, high quantum yield	Koo et al. (2015)
Fe_2O_3 nanoparticles	6–150 nm	Nanocube, nanorod, nanosphere	Magnetic storage, catalysts, sensor manufacturing, drug delivery, magnetic resonance imaging	High magnetic strength	Martínez-Fernández et al. (2016)
ZnO nanoparticles	10–400 nm	Nanocube, nanorod, nanosphere	Sensor manufacturing, wave filters, UV protector, personal care products, coatings, ceramic products	Electronics, anti-corrosion, photocatalyst, UV protector	Ruttkay-Nedecky et al. (2017)

MWCNT, multi-walled carbon nanotube; SWCNT, single-walled carbon nanotube; UV, ultraviolet; TiO_2, Titanium dioxide; Ag, Silver; Au, Gold; CdS, Cadmium sulfide; Fe_2O_3, Iron(III) oxide; ZnO, Zinc oxide

are practiced for detection. Metal and metalloid oxides, sulfides, carbonates, and carbides are ceramic nanomaterials. The nanomaterials mentioned above can be chemically heat resistant, inactive, and feasible for a wide range of operations. Electronics and Chipset exploit semiconductor nanomaterials because of their broad bandwidth. Semiconductor nanomaterials comprise tremendous computing power for mobile devices. These engineered nanomaterials can also be made by applying both metals and metalloids. Semiconductor nanomaterials are used in photoelectron formation, photovoltaics, and photocatalysis along with hydrogen production. Semiconductor nanomaterials are manufactured in various morphologies differing from 0 to 3D configurations since this structure can support tune across the bandgap (Huntingford et al. 2019; Pang et al. 2021).

Carbon-based nanomaterials are composed of carbon nanotubes that have a thermal conductivity similar to diamonds along with elevated electrical conductivity. Carbon nanotubes are applied in hydrogen fuel cell components, pharmaceuticals, and microelectronics. However, there are worries over the health consequences of exposure to carbon nanotubes, which might be similar to the exposure to amosite. Graphene oxide nanoparticles, oxidative by-products of graphene, have been shown to be a recently established and more fascinating nanomaterial for the biomedical industry. Even though the expectation of many applications for graphene oxide fuels has the potential to be further developed, concerns regarding its biosafety for human exposure consequences remain. The latest review has methodically outlined the toxicity studies of graphene oxide both in vitro and in vivo (Fadeel et al. 2018; Qi et al. 2020; Wieszczycka et al. 2021). One more group of carbon-based nanomaterials are polymeric organic molecules, similar to polylactic acid, cellulose, chitosan, polyhydroxyalkanoate, and polyacrylonitrile. These nanomaterials are mainly applied in the medical industry because they are biocompatible and biodegradable (Kolangare et al. 2019).

Commercially manufactured nanomaterials could be released within the aquatic environment at the fabrication phase or end of its life cycle as waste. These engineered nanomaterials could gradually travel to the groundwater and surface of the surrounding environment, or persist in the soil to later be conducted through plants or animal-based food goods (Nagar and Pradeep 2020). Our knowledge of the human health risks associated with engineered nanomaterials in different environmental locations is largely insufficient. There are several reasons for this, including nanoscale size and transient nature of the material, along with dependable overseeing devices that limit the perception of the engineered nanomaterials' effect as contaminants in various water bodies, soil, and air. The above-mentioned knowledge gaps must be discussed to understand discharge and exposure routes of engineered nanomaterials and their lasting health impact.

Nanomaterial exposure and human health impacts

Nanotoxicology is a subset of nanomaterial toxicology and primarily concerns the toxic effects of exposure to nanomaterials. Because the characteristics of material at nanoscale differ, the modifications can produce a surge in effects exclusive to a size-specific regime entirely missing from bulk materials (Laux et al. 2018; Mourdikoudis et al. 2018). Studies on the impact of natural nanomaterials on human health are lacking, and maximum research has focused on engineered nanomaterials. Cronin et al. provided the details of engineered nanomaterials on the human immune system and provided an overview of nanosafety valuation (Cronin et al. 2020). The article mentioned above predominantly concentrates on exposure pathways of numerous nanomaterials from air, water, and food, where nanomaterials are intentionally added, or nanomaterials available in soil are ferried up through food products as primary parameters (Bundschuh et al. 2018). The life cycle of nanomaterials in the human body, their dwelling times, and their fate to various human organs could be distinct and are reliant on the exposure route of the physical and chemical traits of the nanomaterials (Gupta and Xie 2018). The large volume of manufacturing and demanded usage of engineered nanomaterials has elevated several concerns regarding their life cycle as well as developing toxicity to human health.

Exposure of engineered nanomaterials to humans

Due to distinctive characteristics related to their size, engineered nanomaterials have caused a surge in their use in industrialized applications, which in turn has intensified the worries relative to their safety and impact on human health. The need for engineered nanomaterials is thriving among consumers as well as in commercial products such as food additives, water purification, soil cleaning, sunscreen, biocides, supplements, shampoos, agriculture, energy production, feed, veterinary drugs, packaging, and information technology (Martirosyan and Schneider 2014; Kaphle et al. 2018; Yata et al. 2018; Rai et al. 2019). Even though common nanopesticides on the market exceed the 100-nm upper size limit, as nanotechnology exploration develops, it is conceivable that increasing agriculture-affiliated products will fall into the nanoscale size range, lower than 100 nm (Chhipa 2017). This could drive the trophic transposition of engineered nanomaterials to humans along with the potentiality of biomagnification (Judy et al. 2011). In addition, engineered nanomaterials could end up in agricultural

territories throughout their aggregation in sludge during wastewater treatment (Madhura et al. 2019).

The exposure of engineered nanomaterials to humans develops via several pathways such as inhalation, ingestion, dermal penetration, and injection. Figure 1 shows a schematic of the various sources of engineered nanomaterials and their routes of exposure to humans.

Inhalation is the main pathway of exposure to humans; consequently, the existence of nanomaterials in the air poses a substantial health risk (Helland et al. 2008). The recommended threshold exposure limit depends on the density of the nanoparticles. Nanoparticles in the urban air can be multiplied in the nanomaterials manufacturing and processing industries, thus becoming a severe organizational safety problem. It is assessed that nanomaterials are in approximately 3000 products of many applications across various industries (Heinz et al. 2017). Human skin has exclusive barrier characteristics that prevent the penetration of titanium dioxide nanoparticles into the skin. Various studies have shown that titanium dioxide nanoparticles cannot penetrate the skin, even though their size is less than 100 nm. However, other studies have found that titanium dioxide nanoparticles are able to penetrate the skin. However, some of these do not reveal toxicity in particular surroundings.

Engineered nanomaterials including titanium dioxide (80%), zinc oxide (70%), silver (20%), carbon nanotubes, and graphene are known to exist in exclusive skincare and baby products, and thus can be exposed to humans directly when used onto the skin. There is growing controversy over

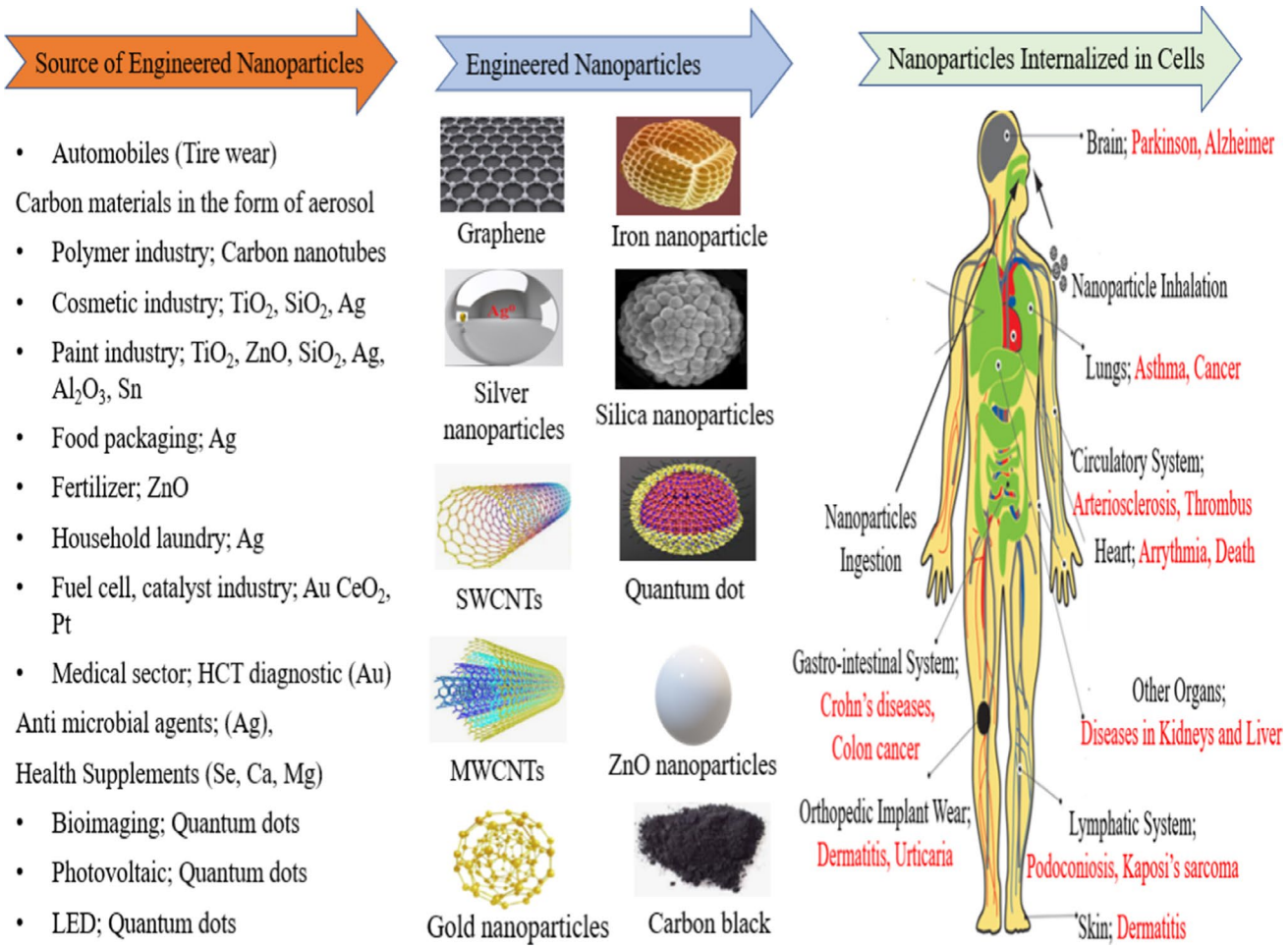

Fig. 1 Examples of possible sources of products containing engineered nanomaterials, and modes of human exposure. The one-of-a-kind size-subordinate physicochemical properties of nanoparticles frequently advance their applications in numerous items; nonetheless, these equivalent special properties additionally lead to extraordinary physiological reactions in living frameworks by communication with these materials. Nanoparticles enter the body by crossing one of their external layers, either the skin or lungs or digestive system. How well they move from outside to inside will rely upon the particles' specific physical and chemical properties. TiO_2: Titanium dioxide; SiO_2: Silicon dioxide; Ag: Silver; ZnO: Zinc oxide; Al_2O_3: Aluminum oxide; Sn: Tin; Au: Gold; Pt: Platinum; CeO_2: Cerium dioxide; HCT: Hematocrit; LED: Light-emitting diodes; Se: Selenium; Ca: Calcium; Mg: Magnesium; SWCNT: Single-walled carbon nanotube; MWCNT: Multi-walled carbon nanotube

this possibility because of the route of engineered nanomaterials over the skin barrier (Alfei et al. 2020). It is commonly believed that metallic engineered nanomaterials penetrate the skin and move to the basal layers. Since the skin's pores are tiny, it is evident that even the smallest particles can pass through easily. Zinc oxide nanoparticles are utilized in the food industry, silver nanoparticles are utilized in the apparel industry for antiseptic and deodorization products, and iron oxide nanoparticles are applied in dyes and jewelry waxing and can be directly exposed to the skin during use (Ajdary et al. 2018; Malakar et al. 2021).

Carbon nanotubes have applications in metal composites, supercapacitors, organic electrolytes, field emission displays, ionic liquids, and lithium batteries. In addition, suitably functionalized carbon nanotubes are also being examined for drug delivery systems and protein transporters. Furthermore, they have the potential to be used in nanoelectronics technology (Bhatia 2016). Graphene-based products are being tried in applications using polymer composites, metal alloys, printed electronics, flexible transparent conductors, filtration systems, multifunctional coatings, oil, etc. (Faruque et al. 2021). The silver nanoparticle coating has been employed in food as an anti-microbial agent along with cellulose pads which are generally incorporated into the containers of meat products (Ahari et al. 2021). The silver nanoparticles are additionally utilized in water purifiers, fabrics, bed linens, toothpaste, shampoos, deodorants, kitchen appliances, and nursing bottles. Consequently, humans can originate direct contact with engineered nanomaterials through food, pharmaceuticals, water filtration, household commodities, cosmetics, etc., leading to oral, dermal penetration, and intravenous exposure pathways (Seltenrich 2013; Halfar et al. 2021; Kannan and Vimalkumar 2021).

Another exposure pathway is the gastrointestinal tract containing food and drink consisting of nanomaterials. For instance, food-grade titanium dioxide nanoparticles may consist of some nano-size particles. They are practiced as oxygen sensors in food packaging. The food dye E171 contains titanium dioxide nanoparticles at concentrations within 1–5 µg/mg. These nanoparticles have also been discovered in candies, gums, dressings and seasonings, non-dairy ointments, and nutritional enhancements. In addition, titanium dioxide and magnesium oxide nanoparticles are applied as food preserving agents and facilitate food handling (Ranjan and Ramalingam 2016). Furthermore, titanium dioxide nanoparticles are used as a colorant in confectionery food items and non-dairy creamers. The quantity of titanium dioxide nanoparticles ingested is predicted to be approximately 0.2–0.7 mg/kg body weight/day in the USA as well as approximately 1 mg/kg body weight/day in the United Kingdom and Germany (Ropers et al. 2017). Winkler et al. reviewed the knowledge gaps in investigating the influences of titanium dioxide nanoparticles as food additives and found that the increased exposure of this food additive might impact kids. In the USA, the evaluated nutritional consumption of titanium dioxide nanoparticles was discovered to be 1–2 mg/kg body weight/day for kids below ten years of age (Winkler et al. 2018). Nevertheless, research was lacking to determine the upper consumption levels for titanium dioxide nanoparticles as a food additive; additional interpretation is required to concentrate on this uncertainty.

The Scientific Committee on Food (SCF) of the European Food Safety Authority (EFSA) has specified a consumption limit of 20–50 mg of silica nanoparticles per 60 kg person (Younes et al. 2018). Silica nanoparticles have been identified in the creation and repository of processed food, and it was noticed that about 43% of amorphous silica is in the nanoscale range (Murugadoss et al. 2017). Silica is perhaps best recognized in anti-caking agents, anti-foaming agents, and refining agents in food. Silica particles are also identified in instant soups, spices, and milk powder at a size of 50–200 nm. Additionally, silica is used as a nanofiller in food wrapping and could be transmitted when it comes in contact with food (Rizvi et al. 2010). Furthermore, silica is broadly exploited in moisturizers and ointments.

Consequently, the oral and dermal penetration, together with the venous exposure of humans to silica nanoparticles, is undoubtedly inevitable. Employees in the manufacturing production of these particles are also vulnerable to exposure by respiration. The medical application of engineered nanomaterials has shown promising outcomes in fighting illness; however, it may likewise have undesirable effects. The rising usage of nanopesticides in food production means that these impurities can bioaccumulate in soil and food plants that can be a possible cause of exposure when ingested. Human ingestion of agricultural foods can provide exposure to significant levels of nanomaterials, where nanomaterials exist in soil could finish up as the final by-product, counting of meat and dairy products along with their toxicological contacts continue to be unclear (Rasmussen et al. 2010).

Circulation and redistribution of engineered nanomaterials in humans

The different exposure routes such as inhalation, ingestion, and dermal penetration carry external nanomaterials toward the human body and, due to their size, can also disturb organisms at the cell level, resulting in types 1, 2, and 3 cell death. It is predicted that the size, charge, and shape of nanomaterials can increase the rate of transference across cell membranes by a factor of 60. Within the pH range of human cells, numerous nanomaterials are able to dissolve and discharge metal ions. Nanomaterials are not simply found in the nasopharyngeal zone; they instantly reach the lungs, increasing the retaining time of nanomaterials in the human body. When nanomaterials are in the lungs, they can

pass the blood-air-tissue barrier and penetrate through to the bloodstream, likely impacting other organs in the body. The dose of nanomaterial by inhalation can similarly induce a severe response, potentially leading to thrombosis, myocardial ischemia, and vascular dysfunction. Inhaled nanomaterial can dwell in the body for three or more months and is excreted out of the body by urine (Miller et al. 2017). The large surface area of the gastrointestinal tract can endorse the adsorption of nanomaterials following their transformation within the bloodstream. Additionally, ingested nanomaterial can dissolve in the stomach's acidic pH, and the discharge of dissolved ions like silver and cadmium nanoparticles can lead to toxic consequences (Huang and Tang 2021).

The size of nanomaterials changes their adsorption rate, as well as lesser particles that can be conducted upward by endocytosis. Once these nanomaterials penetrate the bloodstream, all of them observe an identical pattern in the inhalation exposure route and generate chaos in the organ structures at the cellular and subcellular levels by producing chemically responsive modes. Correspondingly, when nanomaterials penetrate through the skin, the penetration rate into the bloodstream depends on the size, as the smaller nanomaterials permeate more easily and influence separate organs of the body. Exploration has indicated that the nanoscale size of nanomaterials can streamline their effortless at conveyance in the bloodstream and may disturb organs such as kidneys, liver, and lungs; likewise they may be present in the breast milk of breastfeeding mothers (Attarilar et al. 2020). Moreover, their tiny nano-size allows them to cross the blood–brain barrier along with exposure similarly derived in neurotoxicity.

Impact of engineered nanomaterials on human health

Detailed observations on how engineered nanomaterials impact human health are limited. Moreover, there is a little data on employee exposure in industries operating with nanomaterials. Therefore, most investigations in this field have been performed on animal models. However, risk factors in humans are ruled by exposure level, exposure pathways, and the size, type, distribution, reactivity, and shape of the engineered nanomaterials. For employees in conditions of continuous inhalation exposure, it was observed that titanium dioxide nanoparticles displayed a higher indicative no-effect level (INEL) spell out of 17 $\mu g/m^3$, followed by fullerenes. The impact of engineered nanomaterials taken in through respiration depends on their size, shape, characteristics, breathing rate, etc. (Mikkelsen et al. 2011). Engineered nanomaterials in the size range of 10–100 nm collect in the alveolar region, while engineered nanomaterials smaller than 10 nm can aggregate in the thoracic zone. For long multi-walled carbon nanotubes, the clearance mechanism against the lung may sink (Sinis et al. 2018).

Liao et al. monitored 124 engineered nanomaterials-operating employees along with 77 unexposed employees for six months, stating that employees exposed to carbon nanotubes revealed a variation in anti-oxidant enzyme movements for glutathione (GSH) peroxidase-1 (GPX-1) along with lung behavior, and variations were observed in the anti-oxidant enzyme activity for copper-zinc superoxide dismutase (SOD) and cardiovascular markers. This investigation specified that a decreased grade of serum CC16, as well as lung behavior, in employees made them vulnerable to nanomaterials, which was undoubtedly consistent with past investigations (Liao et al. 2014). Furthermore, studies have exhibited that nanomaterials could intrude among the epigenetic mechanism, which incorporates adaptation in gene expression grades without modifications in the genuine DNA itself over methylation, histone tail adaptation, or microRNA mechanisms (Stoccoro et al. 2013; Smolkova et al. 2015). The epigenetic adjustment has been correlated with cancers, cardiovascular complexities, physiological disturbances, autoimmune disorders, neurodegenerative diseases, and psychiatric diseases (Stoccoro et al. 2013). Some detrimental outcomes induced by common engineered nanomaterials during in vivo and in vitro studies are explained below.

Silver nanoparticles

Nanomaterials smaller than 100 nm can penetrate skin cells, those close to 40 nm can move within nuclei, and those less than 35 nm can move across the blood–brain barrier. Additionally, catalytic movement, adsorption rates, and binding capacity may be enhanced in smaller nanomaterials, thereby influencing the dwelling time in the body (Yetisgin et al. 2020). Sahu et al. illustrated that size is the most decisive aspect of the cytotoxicity and genotoxicity of silver nanoparticles in human liver cells (Sahu and Hayes 2017). Prior investigations have demonstrated that oral exposure to silver nanoparticles is able to direct their transference to numerous areas, for example, to the spleen, lungs, bone marrow, kidneys, liver, parathyroid, thyroid, brain, skin, eyes, heart, muscles, small intestine, stomach, prostate, tongue, blood, teeth, duodenum, and pancreas. Investigations with albino mice given dose-reliant silver nanoparticles orally for 21 days revealed weight loss and adversely impacted microvilli and intestinal glands, leading to total reduced ingestion by the intestine. An in vivo study with rats proved that silver nanoparticles are able to be passed on to the offspring, along with the oral administration of silver nanoparticles in dosages higher than 100 mg/kg of body weight/day, which might produce oxidative stress in hepatic tissue in the time of pregnancy (Gaillet and Rouanet 2015).

In a separate research study, the hepatotoxicity and genotoxicity of silver nanoparticles were discovered in female albino rats (El Mahdy et al. 2015). It was found that exposure to silver nanoparticles produced sinusoidal development as well as leukocytosis concerning all in vivo models. It was found that silver nanoparticles could undoubtedly be transmitted to the offspring via the lungs, kidneys, brain, and liver, with high levels presenting when the parent rat orally ingested citrate-covered silver nanoparticles close to 7.9 nm at a concentration of 250 mg/kg/day (Ema et al. 2017). The silver nanoparticles generated phosphorylation of histone H3 at serine 10 (p-H3s10), which could be utilized to assess the toxicity of silver nanoparticles. The authors found that silver nanoparticles integrated within the cells along with the ions discharged were dependable for the phosphorylation (Zhao and Ibuki 2015). The DNA destruction through engineered silver nanoparticles can be explored over the CometChip® single-cell array platform (Watson et al. 2014). This investigation reported DNA destruction in TK6 cells by silver nanoparticles at a concentration of as little as 5 µg/ml, which is disturbing considering that silver nanoparticles are being utilized in anti-microbial products along with elevating the shelf life of food. At a concentration of 20 µg/ml, silver nanoparticles shortened TK6 cell endurance to 27%, conceivably as a result of dysregulation of Bax and Bcl-2 genes (Watson et al. 2014).

Organic preservatives in silver nanoparticles have been shown to regulate the toxicity and stability of engineered nanomaterials. In general, engineered nanomaterials with a positive surface charge may rapidly pass into cells by way of electrostatic attraction, resulting in a long retention time in the human body. Engineered nanomaterials can similarly cause conformational modifications in the bound protein along with influencing its operational functions and inducing diseases such as amyloidosis. The surface charge change can similarly alter additional features, such as aggregation along with hydrodynamic diameter. Transitions in surface traits could disturb the interaction of nanomaterials with cells, tissues, and organs that handle their adsorption. The permanency of engineered nanomaterials in the human body may enhance the dwelling time of nanomaterials as well as increase the toxic effects because of deferred discharge (Li et al. 2021).

Carbon nanotubes and graphene

Carbon nanotubes have been involved in considerable examination because of their unique physical fiber, such as structural and chemical components, and they are foreseen to be broadly utilized in different industries designed for medicine and electronics. In addition, there have been concerns about safety issues involving carbon nanotubes because of their insolubility in the lungs. Mangum et al. found that single-walled carbon nanotubes could produce scratches and interstitial infection in rats within 7–90 days (Mangum et al. 2006). Gomes et al. applied carbon materials such as multi-walled carbon nanotubes, carbon xerogels, and activated carbon to synthesize platinum catalysts, which were applied using the aqueous aniline solvents approach through catalytic air humid oxidation. The synthesized catalysts and materials were investigated using various procedures, including scanning electron microscopy and transmission electron microscopy (Gomes et al. 2004).

Carbon nanotubes produce the same detrimental consequence as asbestos, such as mesothelioma, cancer, pulmonary inflammation, and fibrosis. It has been described that the toxicity enforced by carbon nanotubes is conditioned based on rigidity, route, surface functionalization, method of dispersion, size, impurities, and exposure time. Numerous studies have mentioned that longer carbon nanotubes produced more significant toxicity than shorter ones (Sharma et al. 2016). In mice, multi-walled carbon nanotubes 5–15 µm in length caused fibrosis, considering that shorter lengths in the range of 350–700 nm brought about lower toxicity. Moreover, long multi-walled carbon nanotubes induced inflammation along with genotoxicity (Sharma et al. 2016). The functionalization of multi-walled carbon nanotubes contributes to lowering toxicity. It was determined that carboxylate-functionalized multi-walled carbon nanotubes did not create an inflammatory response. However, substantial cationic functionalization instigated pulmonary fibrosis in a mouse model (Orecchioni et al. 2014). It was described that agglomeration rather than the net charge on the surface of multi-walled carbon nanotubes derived from functionalization is necessary for considering the reduced toxicity of multi-walled carbon nanotubes (Allegri et al. 2016).

The existence of either a carboxyl or amino group lessened toxicity, establishing that the degradation is independent of the net charge on the surface of multi-walled carbon nanotubes. It was further discovered that surface-functionalized multi-walled carbon nanotubes displayed a more considerable inclination of agglomeration than pristine multi-walled carbon nanotubes, which could mean a greater reduced toxicity (Allegri et al. 2016). The excellent mortality rate and malignant mesothelioma were discovered in all rat models made vulnerable to multi-walled carbon nanotubes by intraperitoneal injection. It was perceived that lengthier carbon nanotubes illustrated greater toxicity along with amplified curvature, which is correlated with lower toxicity (Rittinghausen et al. 2014). Bhattacharya et al. introduced a technique for inflammation pathways impacted by carbon nanotubes (Bhattacharya et al. 2013). It was recommended that lengthened carbon nanotubes resulted in activation of nicotinamide adenine dinucleotide phosphate (NADHP) oxidase in macrophages, activating reactive oxygen species generation. However, short carbon nanotubes

were attributed to the macrophages and caused lysosomal destruction resulting in mitochondrial damage and reactive oxygen species creation (Bhattacharya et al. 2013).

Instillation of two categories of multi-walled carbon nanotubes (Mitsui-7 and NM-401) into Muta-mouse adult females indicated enduring fibrotic lesions in the lungs after 90 days of exposure. NM-401 triggered DNA destruction with Mitsui-7, and the DNA destruction was much lower extent. These categories of carbon nanotubes were straight and varied in length and diameter; nevertheless, the surface area for NM-401 was smaller than that for Mitsui-7. Both of these directed to modifications in gene expression correlated alongside carcinogenic transfiguration (Rahman et al. 2017). It ought to be distinguished, those numerous constraints may affect experimental toxicity outcomes in several forms. Some specifications consist of the strain of mice, category of exposure, dosage, and frequency of test sample selection after exposure (Rahman et al. 2017). It was identified that multi-walled carbon nanotubes functionalized along with carboxylic groups for a diameter wider than 40 nm did not influence the cell endurance of macrophages, considering that those alongside an equivalent length but diameter in the range of 15–40 nm displayed confined cytotoxicity, which denotes that cytotoxicity increases along with a decrease in diameter when the lengths are equivalent (Allegri et al. 2016).

Graphene nanosheets were recommended as a supplement in scaffoldings for tissue engineering to strengthen cell accouterment/propagation and were also applied in photothermal cancer therapy along with drug delivery. The size-reliant cytotoxicity of degraded graphene oxide nanoparticles on human mesenchymal stem cells was investigated by applying the fluorescent diacetate assay (Akhavan et al. 2012). It was noticed that the degraded graphene oxide nanoparticles along an average lateral dimension of 11 ± 4 nm revealed low cell vitality at an accumulation of 1 µg/ml after 1 h, considering that degraded graphene oxide nanosheets along an average lateral dimension of 3.8 ± 0.4 µm displayed substantial cytotoxicity at a much more significant accumulation of 100 µg/ml. For the degraded graphene with an average lateral dimension of 11 ± 4 nm, the vitality of all the cells was eradicated after 24 h at an accumulation of 100 µg/ml (Akhavan et al. 2012). This specifies that the nano-sized degraded graphene is more toxic than that at the micron level and exhibits dose-reliant cytotoxicity. It was generally recognized that graphene oxide nanosheets are more toxic than multi-walled carbon nanotubes (Hu et al. 2011). The performance through which graphene oxide nanosheets drive cytotoxicity is by interruption of the cell membrane at the initial contact of the cell with the graphene oxide; hence, the cytotoxicity is separated from the incubation period with cells in vitro. It should be seen that graphene oxide nanoparticles control high affinity concerning protein absorption along with a layer of protein that could mollify graphene, thereby shortening its toxicity (Hu et al. 2011).

Silica nanoparticles

It was realized that silica nanoparticles almost 22.5 nm and 56.9 nm in diameter brought lessened FE1 cell vitality after 24 h of exposure, correlating to nanoparticles of average diameters of 237.5 nm and 2045.4 nm (Decan et al. 2016). The intratracheal silica particles were predominantly cleansed from the lungs, degrading their opportunity to cause a detrimental influence on this organ. Consequently, silica nanoparticles have demonstrated lower toxicity than alternative nanomaterials. Silica nanoparticles have been shown to produce epigenetic transformations, including hypermethylation of apoptosis-corresponding genes within human bronchial epithelial cells as well as hypomethylation of keratinocyte cell lines when exposed to 15-nm silica particles (Mebert et al. 2017). A mutagenic response to silica nanoparticles 7.172 nm and 7.652 nm in size was notified for mouse lymphoma cell lines at 100 and 150 µg/ml (Demir and Castranova 2016). The CometChip® platform review was used to examine the toxicity of amorphous silica nanoparticles, and minor DNA destruction was detected employing this test trial for TK6 cells, except the outcome was not statistically significant (Watson et al. 2014).

Furthermore, it was revealed that there was no reduction in the metabolic movement of TK6 cells when they were exposed to silica nanoparticles (Watson et al. 2014). Although the toxicity of silica nanoparticles is universal, here there was less detection. Liangjiao et al. showed that silica nanoparticles demonstrated toxicity to the immune system (Liangjiao et al. 2019). Silica nanoparticles of size 20–30 nm generated structural transformations to human hemoglobin producing heme displacement and deterioration of the heme protein. Therefore, silica nanoparticles were recommended to generate non-synthetic deterioration of the hemoglobin's heme protein. Moreover, silica nanoparticles displayed dose-reliant cytotoxicity to human lymphocyte cells as well as a half-maximal inhibitory concentration (IC50) of 29 µg/ml. Incubation of human lymphocyte cells with silica nanoparticles at the IC50 for 48 h increased apoptosis as well as necrosis inward toward the cell population (Azimipour et al. 2018).

Titanium dioxide nanoparticles

The oral exposure of titanium dioxide nanoparticles to maternal mice increased the DNA deletion in the fetus, suggesting that it can be passed on to offspring (Trouiller et al. 2009). The oral exposure of female mice of between 25 and 80 nm of titanium dioxide nanoparticles near 5 g/kg brought about a considerably higher inflammation in

the liver, which related to that within male mice, as well as in this study, myocardial and kidney damage because of the nanoparticles correspondingly revealed (Wang et al. 2007). One more study similarly revealed DNA destruction alongside titanium dioxide nanoparticles (21 nm and 50 nm) at 1,000 µg/ml on human embryonic kidney cells (HEK293) along with mouse embryonic fibroblast cells (NIH/3T3), but no oxidative DNA destruction was spotted (Demir et al. 2015). Mice exposed to titanium dioxide nanoparticles in lesser dosages demonstrated a loss of appetite, tremors, and lethargy, which gradually ended (Chen et al. 2009). At a high dosage, these mice revealed intense indications of lethargy, anorexia, tremors, body weight loss, and diarrhea (Chen et al. 2009). A high level of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in mice after exposure to titanium dioxide nanoparticles showed that the latter revealed higher toxicity in the liver than in kidneys (Iavicoli et al. 2012). The International Agency for Research on Cancer (IARC) distinguished pigment grade (lower than 2.5 µm) as well as ultrafine (lower than 100 µm) titanium dioxide nanoparticles as potential carcinogens, considering they could induce inhaling-tract cancer in rats; however, it should be mentioned that no combination among work-related exposure and intensified lung cancer was validated. The toxicity of titanium dioxide nanoparticles to lung cells is subject to their size, shape, form, surface area, and surface chemistry (Iavicoli et al. 2012).

Anatase titanium dioxide nanoparticles caused more toxicity than any other form. In an in vitro study of lung cells, anatase titanium nanoparticles' toxicity was undoubtedly more elevated than in the triple culture model. Different varieties of neurological cells were efficient in internalizing titanium dioxide nanoparticles. Brain microglia cells were exposed to P-25, titanium dioxide nanoparticles. The latter exists in the rutile as well as anatase form. P-25 causes microglia cells to generate reactive oxygen species and has been associated with apoptotic pathways in neurons at a concentration higher than 20 ppm (Long et al. 2006). Moreover, Park et al. showed that with cultured human bronchial epithelial cells (BEAS-2B). It was found that the P-25, titanium dioxide nanoparticles aggregated in the peri-region of the nucleus and enhanced reactive oxygen species revealing the apoptotic process. The introduction of oxidative stress interconnected to genes was also discovered in this study (Park et al. 2008). Titanium dioxide nanofilaments and nanorods may exhibit significant cytotoxicity to epithelial cells. The crystal formation of nanoparticles could influence their toxicity. Additionally, the crystal formation of nanoparticles could transform into ecological matrices, which warrants further intricate toxicity studies.

Gold nanoparticles

Studies have shown that the toxic effects of gold nanoparticles vary by size and that exposure to smaller nanoparticles results in a more pronounced effect. The gold nanoparticles are widely applied in many medical industries; however, they are known to affect human embryonic stem cells, primarily due to their size (De Berardis et al. 2021). Stem cells exposed to 1.5-nm gold nanoparticles displayed less cohesion and impartiality, suggesting cell death, whereas larger nanoparticles at 4 nm and 14 nm size showed no sign of toxicity. Simplifying the size limits of different nanomaterials to endorse toxicity is intricate, as there are presently no standardized toxicity proceedings for scientists to correlate various outcomes. Nevertheless, scientists typically agree that toxicity will surge with smaller-sized nanoparticles, a significant component in stimulating toxicity (Carnovale et al. 2019). The pattern of nanoparticles may similarly be a decisive element in human health properties. For example, fibroblasts exhibited more significant toxicity with gold nanospheres of size 61.46 nm than with smaller diameter nanostars of 33.69 nm. Nevertheless, Steckiewicz et al. (2019) conducted a study involving gold nanorods (39 nm lengths, 18 nm width), nanospheres (6.3 nm), and nanostars (215 nm) exposed to humans and found that gold nanostars are more toxic to human fetal osteoblasts and pancreatic duct cells. Table 2 summarizes the many research results of selected engineered nanomaterials that could impact human health.

Conclusion

With the growing usage of nanomaterials in industries and consumer products, the exposure of nanomaterials to humans and their surroundings continues to rise. The detrimental impact of nanomaterials on human health is predominantly deduced from in vitro and in vivo studies applied to animal models. The exposure of humans to nanomaterials, especially engineered nanomaterials, requires a better understanding of their potential toxicity in order to foresee enduring consequences. Having knowledge of the life cycle of engineered nanomaterials requires significant investigation. Unfortunately, there are inconsistent reports about the toxicity of engineered nanomaterials, typically influenced by several factors that can impact the toxicity study. These factors include the type of cell line, type of nanomaterial, functionalization, synthesis process of the nanomaterials, dosage, size, method of mixing, exposure method, surface charge, shape, gender of the animal model, and cell medium, thus making it exceedingly complicated to determine the risk of engineered nanomaterials or determine their impact on humans. The approach of exposure and potential impact on

Table 2 Research studies on engineered nanomaterials that could impact human health

Nanomaterial	Characteristics	Dosage	Model	Exposure time	Exposure path	Observation	References
Ag nanoparticles	240 nm (diameter)	125–500 μg/kg	IRC mice	1–28 days	Intratracheal instillation	Pulmonary inflammation and granuloma formation	Genter et al. (2012)
Ag nanoparticles	N/A	12.5–200 mg/mL	HepG2 and A549 cells	24 h	N/A	Oxidative damage Upregulated stress-inducible HSPA1A & HO-1	Xin et al. (2015)
Carbon-based MWCNTs	CNT_{small}: 11 nm (diameter), 0.8 ± 0.1 μm (length) CNT_{large}: 67 nm (diameter), 4 ± 0.4 μm (length)	0, 18, 54 or 162 μg/mouse	C57BL/6 mice (female)	24 h, 3 days, and 28 days	Intratracheal instillation	Increased bronchoalveolar lavage fluid for intracellular flow Changed mRNA grades of chemokines CCLs and CXCLs	Poulsen et al. (2015)
Carbon-based MWCNTs	5–15 nm (diameter) 0.1–10 mm (length)	0.5 and 2.5 mg/m^3	Wistar rats (male)	90 days	Inhalation	Multifocal granulomatous inflammation in lungs Diffused histiocytic and neutrophilic inflammation, and intra-alveolar lipoproteinosis	Ma-Hock et al. (2009)
Carbon-based MWCNTs	5 nm (diameter) 5 mm (length)	0.5, 2 and 5 mg/mouse	Sprague Dawley rats	60 days	Intratracheal instillation	Pulmonary inflammation and granuloma formation Injured fibrotic lung	Lanone (2013)
Carbon-based MWCNTs	10–30 nm (diameter)	20 mg/kg	Pregnant mice	10 days	N/A	Induced maternal body weight gain Induced abortion rates dependent on pregnancy times	Qi et al. (2014)
Carbon-based SWCNTs	1–4 nm (diameter)	0, 10, 20 or 40 μg/mouse	C57BL/6 mice (female)	1, 3, 7, 28 and 60 days	Intratracheal instillation	Acute inflammation Progressive fibrosis and granulomas	Shvedova et al. (2005)
Carbon-based SWCNTs	1–4 nm (diameter)	10–40 μg/mouse	C57BL/6 mice (female)	1–60 days	Pharyngeal aspiration	Pulmonary inflammation and granuloma formation Multifocal granulomatous pneumonia and interstitial fibrosis	Shvedova et al. (2008)

Table 2 (continued)

Nanomaterial	Characteristics	Dosage	Model	Exposure time	Exposure path	Observation	References
Carbon-based SWCNTs	10–500 nm (diameter)	0.1 or 0.5 mg/mouse	B6C3F$_1$ mice	7 and 90 days	Intratracheal instillation	Pulmonary inflammation and granuloma	Lam et al. (2004)
						Mild to moderate inflammation with high-dose quartz	
Carbon-based fullerene	50–200 nm (diameter)	28 µg/mouse	Sprague Dawley rats	24 h	Intratracheal instillation	Increased vasoconstriction	Thompson et al. (2014)
						Impaired vasodilation	
Carbon black	14 nm (diameter)	0.018, 0.054 and 0.162 mg	C57BL/6 mice (female)	28 days	Intratracheal instillation	DNA strand breaks in bronchoalveolar lavage and lung epithelial cells	Bourdon et al. (2012)
						Increased plasma low-density lipoprotein	
						Increased total hepatic cholesterol	
Graphene nanoparticles	5 nm (diameter)	50 µg/mouse	C57BL/6 mice (female)	1–7 days	Pharyngeal aspiration	Inflammation in lungs and pleural spaces	Schinwald et al. (2012)
						Frustrated?? phagocytosis	
Silica nanoparticles	70 nm (diameter)	0.2, 0.4 and 0.8 mg/mouse	Pregnant mice	1 and 2 months	Intravenous injection	Linked to structural and functional abnormalities in placenta	Yamashita et al. (2011)
Silica nanoparticles	115 nm (diameter)	8 mg/kg	C57BL/6 mice (female)	1 and 2 months	Intranasal instillation	Detection of deposition in medial prefrontal cortex and hippocampus	You et al. (2018)
						Increased tau phosphorylation and neuroinflammation	
Silica nanoparticles	12 nm (diameter)	975.9, 1030.5 and 1000 mg/kg	Sprague Dawley rats	13 weeks	Oral administration	Increased incidence of lymphocyte infiltration in liver, particularly portal inflammation	Yun et al. (2015)
						Induced liver toxicity, including bile duct hyperplasia and increased foci	

Table 2 (continued)

Nanomaterial	Characteristics	Dosage	Model	Exposure time	Exposure path	Observation	References
TiO_2 nanoparticles	24 nm (diameter)	0, 2, 10 and 50 mg/kg	Sprague Dawley rats	30 and 90 days	Oral administration	Increased diastolic blood pressure Reduced heart rate Injured cardiac function	Chen et al. (2018)
TiO_2 nanoparticles	21 nm (diameter)	150 mg/kg	C57BL/6 mice (female)	Once a week, 6 weeks	Oral administration	Subtle response with alterations in liver	Husain et al. (2015)
TiO_2 nanoparticles	N/A	1, 5, or 10 µM/well	NHBE cells	8 and 24 h	Intratracheal instillation	Increased Bradykinin, ATP, and CGRP in NHBE cells	Kim et al. (2020)
		200 $\mu g/m^3$	BALB/c mice	21–23 days		Substance P, ATP, and CGRP increased in bronchoalveolar lavage fluid	
TiO_2 nanoparticles	N/A	0.324, 648, 972, 1296, 1944 and 2592 mg/kg	Adult mice	24–48 h, 7–14 days	Intraperitoneal injection	Ruptured spleen Swollen renal glomeruli Elevated levels of enzyme's alanine aminotransferase and aspartate aminotransferase	Chen et al. (2009)
TiO_2 nanoparticles	30 nm (diameter)	106 s/cm^2, 108 s/cm^2 and 1010 s/cm^2	Caco-2/HT29-MTX cell	4 h, 5 days	Ingestion	Affected intestinal epithelial cells Reduced surface area for nutrient absorption	Guo et al. (2017)
TiO_2 nanoparticles	N/A	5, 50 and 150 mg/kg	Adult mice	30 days	p38 and c-Jun n-terminal kinase signaling pathways	Ruptured spleen Increased accumulation of ROS in spleen	Wang et al. (2011)
TiO_2 nanoparticles	N/A	5, 50 and 500 mg/kg	Adult mice	24 h, 7–14 days	Oral administration	Persistent inflammation, apoptosis, and oxidative stress Led to induction of chronic gastritis	Mohamed (2015)

Table 2 (continued)

Nanomaterial	Characteristics	Dosage	Model	Exposure time	Exposure path	Observation	References
TiO_2 nanoparticles	5 nm (diameter)	62.5, 125 and 250 mg/kg	Adult mice	30 days	N/A	Decreased body weight, and increased coefficients of liver, kidney, spleen, and thymus Damaged liver function Observed blur in large area and congestion in liver tissue	Duan et al. (2010)
TiO_2 nanoparticles	25 and 80 nm (diameter)	5 g/kg	Adult mice	14 days	Oral administration	Altered activity of LDH and alpha-HBDH in blood serum Damaged cardiac muscle No pathological lesions found in heart, lung, and splenic tissue	Wang et al. (2007)
TiO_2 nanoparticles	N/A	0, 10, 50 and 200 mg/kg	Sprague Dawley rats	30 days	N/A	Decreased activity of HBDH and CK Damaged cardiac muscle	Wang et al. (2013)
Au nanoparticles	20 nm (diameter)	3 µg/mouse	Wistar rats (male)	1–60 days	Intravenous injection	No Au accumulation found in brain Significant effects on genes related to detoxification, lipid metabolism, cell cycle, defense response, and circadian rhythm	Balasubramanian et al. (2010)
Au nanoparticles	4–5 nm (diameter)	20 $\mu g/m^3$	Sprague Dawley rats	90 days	Inhalation	No translocation to distal organs No pulmonary inflammation Accumulation of gold in only lungs and kidneys	Sung et al. (2011)

Table 2 (continued)

Nanomaterial	Characteristics	Dosage	Model	Exposure time	Exposure path	Observation	References
Au nanoparticles	N/A	0–50 mM	Bovine endothelial cells (GM7373)	96 h	N/A	Induced toxicity detected in XTT-assay Dose-dependent sensitivity of spermatozoa	Taylor et al. (2011)
Fe_2O_3 nanoparticles	28–30 nm (diameter)	10 mg/kg	Pregnant CD-1 mice	1–3 days	N/A	Increased fetal deaths and accumulation of iron in fetal liver and placenta Greater bioaccumulation and toxicity with positively-charged surface coating	Di Bona et al. (2014)
Fe_2O_3 nanoparticles	20 and 280 nm (diameter)	0.8 and 20 mg/kg	Sprague Dawley rats	30 days	Intratracheal instillation	Pulmonary inflammation and granuloma formation Pathological damage in stomach, liver, heart, and spleen	Wang et al. (2008)
ZnO nanoparticles	~ 10 nm (diameter)	0.5, 1.0 and 2.0 mg/m^3	Human volunteers	4 h	Inhalation	Increased body temperature, serum acute-phase proteins, and neutrophils Metal fume fever	Monsé et al. (2018)
ZnO nanoparticles	20–50 nm (diameter)	0.2–0.4 mg/mL	Wistar rats (male)	1, 24, 72 h and 7 days	Intratracheal instillation	Increased oxidative stress in lungs Increased ROS level	Horie et al. (2014)
ZnO nanoparticles	13 nm (diameter)	133.3, 200 and 300 mg/kg	ICR mice	10 days	Oral administration	Enhanced maternal–fetal transfer of both pollutants and aggravated embryotoxicity Elucidation of synergistic embryotoxicity	Teng et al. (2020)

Table 2 (continued)

Nanomaterial	Characteristics	Dosage	Model	Exposure time	Exposure path	Observation	References
ZnO nanoparticles	50 nm (diameter)	600 mg/kg and 1 g/kg	Wistar albino rats	5 days	Oral administration	Increased serum inflammatory cytokines Increased calcium concentration in heart Damaged DNA	Abdel Baky et al. (2013)
Quantum dots modified CdS	1.67, 2.59 or 3.21 nm (diameter)	5, 10, 20 mg/kg	Pregnant mice	20 days	Inhalation	Decreased survival rate, body length, body mass Ossification of limbs	Zalgeviciene et al. (2017)
Quantum dots modified CdS	N/A	5,1 nmol/rat	Sprague Dawley rats	24 h	Inhalation	Limited chronic toxicity against offspring over the long term Severe growth inhibition and 71.08% offspring mortality with high-dose QDs	Yang et al. (2018)
Quantum dots modified CdS	N/A	10, 7.5, 5, 2.5 and 1.0 μM	HEK293 cell line	24, 48 and 72 h	N/A	Toxicity linked to surface structures and physicochemical properties	Zheng et al. (2012)

Ag, Silver; HSPA1A, heat shock protein A1A; HO-1, heme oxygenase 1; MWCNT, multi-walled carbon nanotube; CNT, carbon nanotube; mRNA, messenger RNA; CCL, chemokine (C–C motif) ligand; CXCL, chemokine (C–X–C motif) ligand; SWCNT, single-walled carbon nanotube; TiO_2, Titanium dioxide; NHBE, normal human bronchial epithelial; ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; ROS, reactive Oxygen Species; HBDH, α-hydroxybutyrate dehydrogenase; LDH, lactate dehydrogenase; CK, creatine kinase; Au, Gold; Fe_2O_3, Iron(III) oxide; ZnO, Zinc oxide; CdS, Cadmium sulfide

humans has been reviewed here. Dynamic action may prevent engineered nanomaterials from passing through human skin and lessen their impact on human health. However, the toxicological consequences of exposure to engineered nanomaterials are far from clear. The latest scientific studies have helped to better understand the connections of engineered nanomaterials to cells, tissues, and organs. As with any group of hazardous toxins, several exposure routes must be inspected, and more research is necessary to assess the impacts of engineered nanomaterials on human health. It is very important to improve standard test modes for inspecting the toxicity of nanomaterials in vitro and in vivo by utilizing animal models. A more vigorous technique for identifying the risks of engineered nanomaterials will be required in the near future, as various types and vast amounts of engineered nanomaterials alter the direction of commercialization.

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