Health implications of engineered nanoparticles in infants and children

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Background: **The nanotechnology boom and the ability to manufacture novel nanomaterials have led to increased production and use of engineered nanoparticles (ENPs). However, the increased use of various ENPs inevitably results in their release in or the contamination of the environment, which poses significant threats to human health. In recent years, extraordinary economic and societal benefits of nanoproducts as well as their potential risks have been observed and widely debated. To estimate whether ENPs are safe from the onset of their manufacturing to their disposal, evaluation of the toxicological effects of ENPs on human exposure, especially on more sensitive and vulnerable sectors of the population (infants and children) is essential.**

Data sources: **Papers were obtained from PubMed, Web of Science, and Google Scholar. Literature search words included: "nanoparticles", "infants", "children", "exposure", "toxicity", and all relevant cross-references.**

Results: **A brief overview was conducted to 1) characterize potential exposure routes of ENPs for infants and children; 2) describe the vulnerability and particular needs of infants and children about ENPs exposure; 3) investigate the current knowledge about the potential health hazards of ENPs; and 4) provide suggestions for future research and regulations in ENP applications.**

Conclusions: **As the manufacturing and use of ENPs become more widespread, directed and focused studies are necessary to measure actual exposure levels and to determine adverse health consequences in infants and children.**

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Key words: **developmental effects; human exposure; maternal-fetal transmission; nanopediatrics; nanotoxicity**

Review article

Introduction

Nanotechnology and nanoparticles

Nanotechnology involves the deliberate production and application of nanoparticles (NPs) between 1 and 100 nm.[1] The emergence of nanotechnology began in the 1980s,[2] and currently, applied nanotechnology is a sharply growing market producing various engineered NPs (ENPs) with different chemical composition, size, crystal structure, shape, surface chemistry, and charge.[3,4] These ENPs can be classified by their dimensionality, morphology, composition, and uniformity and agglomeration state.[5] The physical, optical, thermal, chemical, and biological properties of ENPs are different and yield more effective performance compared to their respective bulk substances.[6] Hence, ENPs are now being used in various commercial products ranging from electronics to medical and health care products, food, textiles, and household products.[7] As of January 2014, the publicly available online inventory of ENP-based consumer products contained 1682 products (Fig. 1), and by 2015, the market for nanoproducts will reach the $1 trillion milestone.[8]

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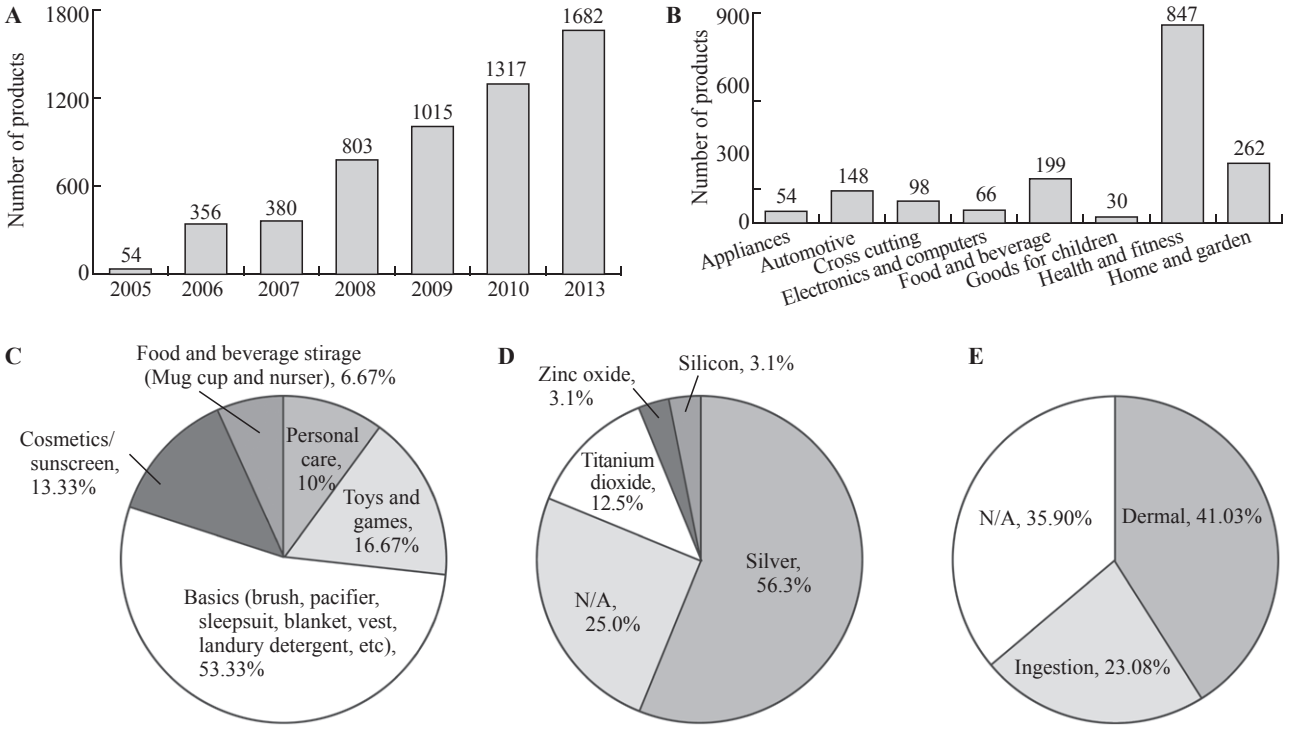

Fig. 1. A: The number of total nanotechnology-based consumer products listed by date of inventory update (http://www.nanotechproject.org/cpi/); **B:** The number of products according to categories based on classification. The category goods for children includes 30 products; **C:** Percentage of products per sub-category within the category goods for children; **D:** Percentage of NPs mentioned in the product descriptions within the category goods for children; **E:** Percentage of the potential exposure pathways from a theoretical perspective, according to each product's intended use within the category goods for children. NPs: nanoparticles; N/A: not available.

Environmental, health, and safety concerns of ENPs

As applications of nanotechnology expand and nanoproducts are used more frequently, ENPs are released into the air, soil, and water and become "emerging pollutants". Their small size and high reactivity have raised environmental health and safety concerns about their transport, fate, and toxicity in the environment and risks to human health.[9,10]

Possible scenarios of infants and children exposure to ENPs

Exposure of children to ENPs can occur through inhalation, ingestion, and/or dermal exposure, from contaminated air, food or drinking water, or directly from nanoproducts (Figs. 1 and 2).[11-13] Children's consumer products were ranked based on their bioavailability of silver NPs (AgNPs). Products from greatest to least were: plush toy and fabric products, cleaning products, sippy cups, humidifiers, breast milk storage bags, and kitchen scrubbers.[11] However, the extent of ENP exposure is unknown.

Inhalation

Exposure near manufacturing or construction sites

Because of greater concentrations and exposure

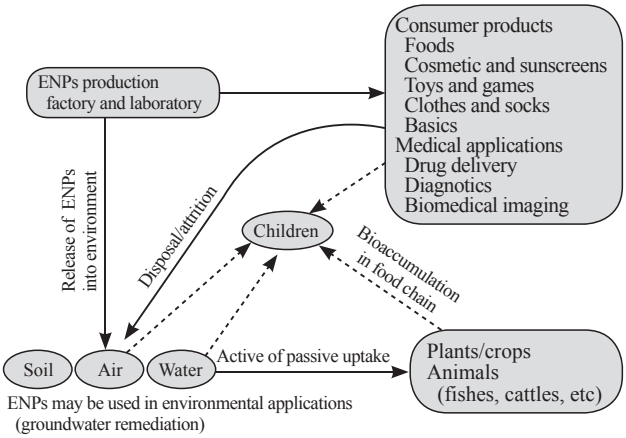

Fig. 2. Potential release, exposure, and uptake of ENPs in children. ENPs: engineered nanoparticles.

frequency of ENPs in occupational settings, the production of ENPs poses risks to workers in the manufacturing facilities.[14] Over 100 nanoproducts mainly containing silicon dioxide (SiO_2)-, zinc oxide (ZnO)-, aluminium oxide-, Ag-, and titanium dioxide (TiO_2)-NPs are used in the construction industry, with measurements from European workplaces confirming a modest exposure of workers to ENPs.[15] In Bangkok, Thailand, there are 400 000 children, aged 0-3, who play in and near those

construction sites.[16] Since airborne ENPs can remain suspended over extended time periods and traverse long distances from the point source, children who live or play around manufacturing or construction sites could encounter elevated levels of ENPs.

Exposure by use of nanosprays

Children can be exposed to nanosprays or nanopowder products for anti-microbial or personal hygiene as the evaporation from the sprayed droplets can form clusters of ENPs which can be inhaled.[12,17,18] These products, including antiodor spray for hunters, surface disinfectant, and throat spray, can emit 0.24 to 56 ng Ag in aerosol-form with a diameter range of 1 to 2.5 μm.[12]

Exposure by playing on synthetic turfs

Artificial surfaces are commonly installed in playgrounds and stadiums.[19] Most synthetic turfs and rubber mulches use pulverized and recycled vehicle tires as padding and grit material, which contain carbon black NPs and carbon nanotubes (CNTs).[20,21] As children crawl, sit, and play on these surfaces, ENPs can be disrupted and released into the atmosphere, where they can be inhaled. Unfortunately to date, there are no studies investigating potential risks and health consequences from this unprecedented, often chronic exposure of ENPs in children playing on tire crumb surfaces and facilities.

Dermal

Exposure through sunscreens and cosmetics

Mainly C_{60}-, TiO_2- and ZnO-NPs are now accepted as additives in pharmaceutical and cosmetic formulations to enhance drug delivery, treat skin disease, or facilitate systemic access.[22,23] Approximately 21 to 60 μg/L of Ti has been found in children's swimming pools, most likely from sunscreen.[24]

Exposure through textiles and clothing

Fabric and textile industries employ ENPs, mainly AgNPs, as an antimicrobial agent.[25] In general, clothing has a moderate Ag content of 30 to 45 μg Ag per gram product.[25] About 13.8 and 23 μg/m^2 of Ag were transferred from the surface of plush toys and baby blankets onto dermal wipes, respectively, which was an initial estimate of the amount of dermal exposure to infants or children.[11,26] The use of AgNPs in wound bandages renders another exposure potential because the product will be in contact with compromised skin.[26,27] Children have been thereby exposed to ENPs through direct contact with the skin, or indirectly when ENPs contained in cloths, fabrics, and sunscreen are released into the aquatic environment.[25,28]

Ingestion

Exposure through nanofoods

ENPs are being added into food and food supplements (nanofood) or food packaging to improve texture, structure, sensory appeal, and extend shelf life.[3,29] According to the inventory of ENP-based consumer products, 205 foods contained ENPs in 2014 (Fig. 1), and 150-600 nanofoods and 400-500 nanofood packaging applications are currently on the market.[30] Foods containing TiO_2-NPs include candies, sweets, cookies, and gums, with gum containing the greatest concentrations.[31] Further intake estimation indicated that 95% of TiO_2-NPs were swallowed by gum consumers after chewing for 10 minutes.[13] For US children under the age of 10, the simulated exposure to TiO_2-NPs was 1-2 mg/kg body weight per day,[31] highlighting the need for the development of methods to study the size distributions and elemental compositions of food-relevant NPs.

Exposure through food chain

Beyond direct exposure, ENPs can translocate into higher orders of the food chain. Certain ENPs end up in the soil with the potential to enter food sources. The absorption, translocation, accumulation, and biotransformation of metal (ZnO and cerium dioxide)-NPs and carbon-based ENPs have been identified in edible plants.[32,33] It is important to identify whether various sizes, types, and chemical compositions of ENPs can be absorbed by soil and transformed or metabolized by different plant species.

Maternal-fetal transmission

Prenatal exposure

Many ENPs [gold-NPs, TiO_2-NPs, SiO_2-NPs, single-walled-CNTs (SWCNTs), and quantum dots (QDs)] can penetrate the placental barrier and concentrate in the fetus.[34-36] The chemical composition, size, charge, dose, and capping materials of ENPs contribute to their ability to translocate from mother to pups across the placental barrier, allowing to induce embryo-fetal toxicity.[36,37] In fact, it has been suggested that ENPs might cross the human placenta because of the transplacental capability of NPs demonstrated in a human *ex vivo* model.[38]

Postnatal exposure via breast milk

ENPs can also transfer from lactating mother to offspring through breast milk. This has been investigated in female rats, showing the total accumulation of polyvinylpyrrolidone coated AgNPs in milk was greater than 1.94% of the intragastrically administered dose after 48-hour lactation.[39] Greater than 25% of AgNPs was absorbed by the digestive tract of infant rats, and 17.9% and 0.9% of the total amount in infant rats was

distributed to the liver and kidney, respectively.[39]

Nanopediatrics

Lipid-based nanocarriers have the ability to effectively deliver therapeutic and imaging agents, and are outstanding in nanomedicine applications.[40] In fact, the global nanomedicine market is expected to grow to $96.9 billion by 2016.[41] Nanopediatrics is a newly emerged branch of pediatrics, which focuses on the development and use of nanomedicine to promote children's health in various areas, including disease diagnosis and treatment.[42] Despite the great promise in these applications, they create additional exposure routes to children.

Review article

Special aspects of physiology and toxicology in infants and children

Differences in exposure between children and adults

Children, a generally vulnerable and high-risk population for a multitude of toxicants, interact in and with the environment in various ways that differ from adults.[43] Children eat more food, drink more water, and inhale more air than adults based on body weight.[44] Children also have greater dermal exposure to ENPs in sunscreens/cosmetics than adults as they have lower body weights but an increased ratio of body surface area to weight.[4] Additionally, three typical characteristics of infants and children further magnify exposure: 1) regular hand-to-mouth behaviors; 2) unique food consumption patterns,[45,46] for example, a child consumes 2-4 times as many TiO_2-NPs as an adult from the consumption of sweet products;[31] and 3) being closer to the ground where aerosolized ENPs in nanosprays with a greater density than air become closer in proximity. Therefore, infants and children are at greater risk of exposure to ENPs compared with adults.[43]

Differences in developmental biology between children and adults

Children are not simply little adults. Anatomy, physiology, and organ function of children all differ from those of adults. The thinner and under-keratinized epidermis of children may increase the absorption of ENPs through the skin. Infants and children are prone to enhanced deposition of inhaled ENPs in the lung because of the relative smaller caliber airway and higher ventilation requirements.[43] Moreover, their immature alveolar epithelium has reduced function, which allows ENPs to pass through blood-air barrier more easily.[43,47] The respiratory rate, heart rate, metabolism, and excretion of children are notably different.[45,48] Infants and children are biologically susceptible and at an increased risk of toxicant injury. This vulnerability arises from developmental immaturities of vital organs, which present unique targets not accessible in adults.[48,49] Particularly in the first months of infancy, the inability to metabolize, detoxify, and excrete toxicants can increase the risk of toxicant injury.[44]

Differences in health effect between children and adults

Toxicological data showed no adverse effect between adults and children because of developmental differences.[43,50] Based on reproductive and developmental toxicology data, timing of exposure, duration, dose and susceptibility, or genotype of parents and fetuses or children plays critical roles in the pattern of injury, with periods of significant vulnerability at both the fetal and early post-natal life stages.[43,50,51] Certain ENPs are able to induce different health risks at different ages. A comparative toxicity study has reported the different responses of TiO_2-NPs on youth and adult rats after 30 days oral exposure.[52] In youths, liver edema, heart injuries and non-allergic mast cell activation in the stomach were observed, with only slight injuries of the liver and kidney, whereas, in adults, reduced intestinal permeability and molybdenum contents were detected.[52]

In infants and children, the growth and development of organ systems are not well adept at repairing damage caused by toxicants, increasing vulnerability where the resulting dysfunction in development can be permanent.[44,46,48] Hence, the delicate developmental processes of fetuses or children may be easily altered by ENPs; if their central nervous system (CNS) is injured, respiratory system damaged, reproductive development disrupted, or immune system development destroyed, the consequential dysfunction could be irreparable. Furthermore, numerous diseases initiated by toxicants require many years to develop, thus toxic exposures that occur early in life are more likely to cause lasting effects than exposures that occur later in life.[45,46,48]

Adverse health effects and potential risks of ENPs

The toxicities of ENPs are a matter of various mechanisms, including: 1) size;[53] 2) charge; 3) shape; 4) surface chemistry/coating;[54] and 5) reactive oxygen species (ROS) generation.[55] Currently, toxicokinetic and toxicodynamic data, as well as the potential health hazards for infants and children are limited and remain under investigation (Fig. 3).

Skin

ENPs such as iron (5 nm),[56] TiO_2,[57] QDs,[58] and AgNPs (25 nm)[27] have previously demonstrated an ability to penetrate the skin barrier, and pose risk of ROS-mediated skin aging.[59] Porcine skin after 14

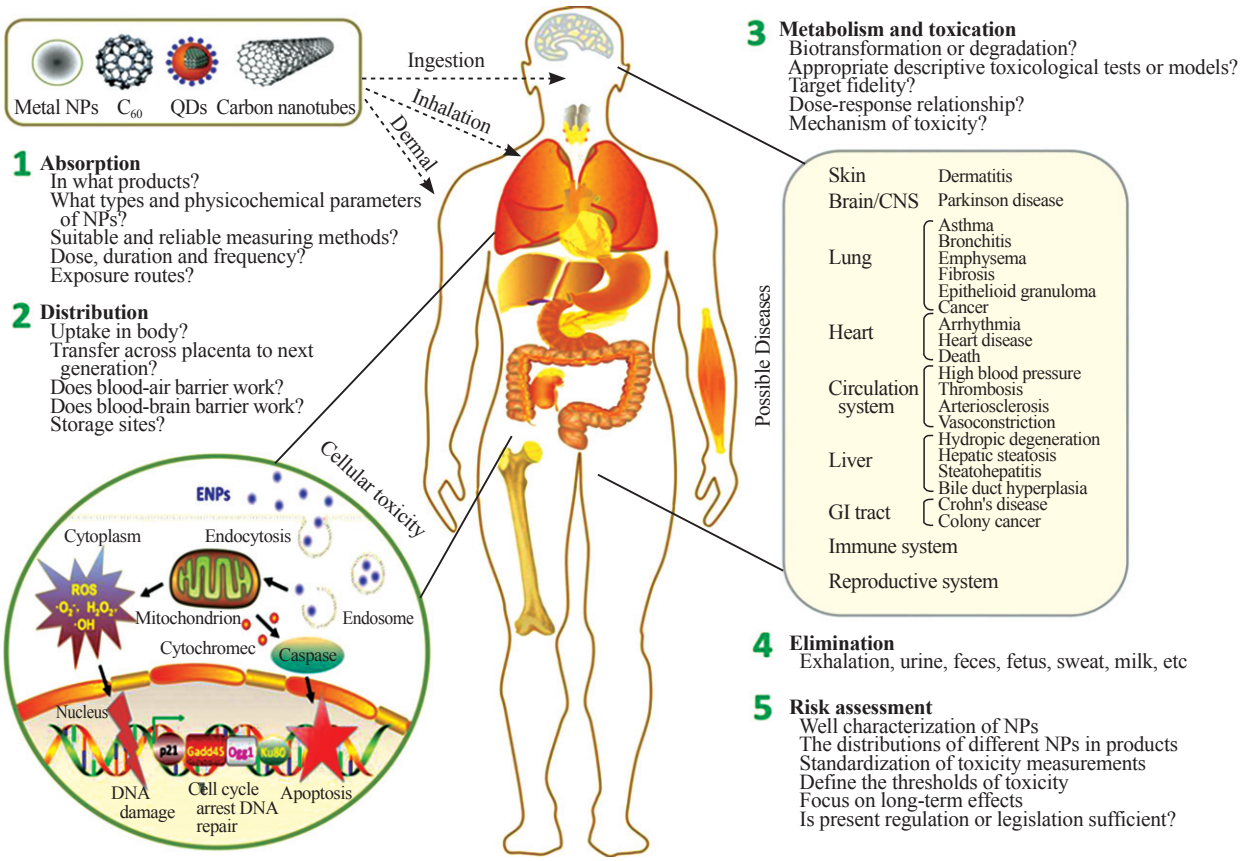

Fig. 3. Knowledge gaps intoxicokinetic, toxicodynamic, and risk assessment data on ENPs in infants and children. Possible diseases were mainly based on a previous review.[5] NPs: nanoparticles; QDs: quantum dots; ENPs: engineered nanoparticles; ROS: reactive oxygen species; CNS: central nervous system; GI: gastrointestinal; O_2: oxygen; H_2O_2: hydrogen peroxide; OH: hydroxyl; p21: cyclin-dependent kinase inhibitor 1; Gadd45: growth arrest and DNA-damage-inducible protein 45; Ogg1: 8-oxoguanine DNA glycosylase; Ku80: X-ray repair cross-complementing 5.

days of exposure to AgNPs demonstrated intercellular epidermal edema with focal dermal inflammation (spongiosis), epidermal hyperplasia, and parakeratosis in a dose dependent manner.[60,61]

Skin penetration can lead to systemic exposure and development of lesions by ENPs.[62,63] It was reported that that a 17-year-old boy with 30% burned skin developed hepatotoxicity and argyria-like symptoms after treatment with an Ag-containing wound dressings.[62] The different systemic toxicities of AgNPs via acute (3 days) and subchronic (13 weeks) dermal exposure were detected in 5-6 week old male guinea pigs.[64,65] Subchronic exposure resulted in greater tissue abnormalities than acute exposure.[64] Uptake of AgNPs by tissue is ranked in the sequence of kidney>muscle>bone>skin>liver>heart>spleen.[65] Therefore, evidence suggests certain ENPs are able to penetrate children's skin and distribute to tissues after prolonged dermal exposure.

Respiratory system

ENP deposition, as an indispensable step for adverse effects, strongly depends on size and shape.[17] Inhaled airborne NPs between 5 to 50 nm are efficiently deposited in the alveoli where risks for toxic effects are the greatest.[17] Childhood exposure to particulate matter of air pollution has been associated with decreased lung function, wheezing, cough, and exacerbation of asthma.[66,67] Because of a large surface area in the lung and the small size of NPs, airborne NPs can penetrate the thin blood-air barrier to reach systemic circulation and efficiently transfer and translocate to other organs.[43,68]

Regarding AgNPs-containing nanosprays, the exposure modeling estimates 70 ng of Ag deposits in the respiratory tract, with 82% falling in the nasopharyngeal region, 2% in the tracheobronchial region, and 16% in the alveolar region, if 1 to 2 throat sprays occurred per day.[12] As nanotechnology-related consumer products develop in popularity and necessity, simultaneous exposure from various types of AgNPs-containing products would be possible and might result in additive exposure levels in children.

Human epidemiological studies and case reports

revealed that long-term exposure to NPs might cause lung damage. The first "nano scare" was reported in March of 2006.[69] About 100 German consumers had symptoms including coughing, headache, sleep disruption and vomiting after using aerosols like bathroom cleaning Magic-Nano products (Kleinmann GmbH; Sonnenbuehl, Germany), though the illness was not linked to the nano-component (ZnO) of the aerosols.[69] A 26-year-old female chemist handling nickel NPs developed throat irritation, nasal congestion, "post nasal drip", facial flushing, and skin symptoms,[70] whereas a 38-year-old healthy man died 13 days after inhaling nickel NPs (<25 nm found in lung macrophages) due to adult respiratory distress syndrome.[71] Another patient reported a 33-year-old woman inhaling carbon NPs from toner dust; she developed weight loss and diarrhea.[72] Case reports confirmed that inhaled ENPs can travel systemically via lymphatic and blood vessels and affect other organs.[71] Published results have illustrated that further research is necessary to better understand the possible biomarkers that could be used for surveillance of ENPs exposure, and to explore nanotoxicological mechanisms by which NPs can cause adverse health effects and most effective ways to protect children.[73]

The gastrointestinal tract (GIT) and liver

Absorption via the GIT is a significant route of ENPs exposure after ingestion of food and pharmaceuticals.[29] GIT is covered by a protective mucosal layer, which is a mixture of highly branched glycoproteins and macromolecules and is a barrier for ENP uptake.[74] After translocation across the intestinal epithelium, ENPs enter the blood stream by hepatic portal circulation to the liver and systemic circulation or by mesenteric lymph nodes to the lymphoid circulation.[74,75] Uptake and distribution can be affected by composition, size, surface coating, surface charge, shape (aspect ratio), and flexibility.[74,75] ENPs can result in hepatic damage and toxicity, as AgNPs can induce a higher incidence of bile-duct hyperplasia, with necrosis, fibrosis, and pigmentation in rats.[76] TiO_2-NPs can cause hepatic injury, thrombus, tachycardia, systolic hypertension,[77,78] nephrotoxicity and pathological changes in mice kidneys.[79] Exposed rats demonstrated reduced liver weight, hepatocyte enlargement, sinusoidal dilatation, and accumulation of granular material.[80,81]

Brain

ENPs have the potential to penetrate the blood-brain barrier and contribute to damage of brain tissues. *In vivo* studies revealed ENPs (metallic NPs, QDs, and CNTs) can be translocated to the brain from the skin, blood, and respiratory pathways.[82] In a cross-sectional study, workers handling ENPs showed a decrease in capability of backward memory in neurobehavioral tests.[83] In children, motor, cognitive, and behavioral changes are observed after particulate metal exposure.[84] These evidences support concerns regarding the neurotoxicity of ENPs, and indicate that children, in particular, may be at an elevated health risk post-NP exposure, since childhood and adolescence are quite crucial periods of neurodevelopment.[84]

Immune and circulation systems

ENPs can interact with complex networks of immune cells located within and beneath epithelial surfaces.[43] ENPs can act as allergens during the neonatal period, triggering the immune system to induce allergic inflammation in later life stages.[43,85] Detrimental cardiovascular consequences due to NPs exposure have been reported in epidemiological studies.[83,86] Cardiovascular disease markers fibrinogen, vascular cell adhesion molecule levels, and interleukin-6 were significantly higher in workers handing ENPs than in unexposed controls, which were consistent with cardiotoxicity of NPs.[83,87] Cationic dendrimers can exhibit significant hemolytic and hematological toxicities.[88] To circumvent toxicity, there is a great need to adopt various strategies, including masking of cationic charge of dendrimers through surface engineering by neutralization of charge.[88]

Reproductive and developmental systems

Pre-pregnancy, pregnancy, prenatal, and postnatal toxicants exposures are avenues offering critical windows of opportunity for adverse reproductive and developmental outcomes,[46] which can be manifested at different phases within the life span of the organism. Both *in vitro* and *in vivo* studies have displayed that metallic NPs, carbon-based NPs, and dendrimers are able to induce adverse effects including reproductive failure, metabolic syndrome, and cancer.[89] Certain ENPs may also have effects on human reproduction by altering testicular and ovarian structure and function.[90,91]

ENPs can induce adverse effects on developing fetuses due to maternal NP exposure and transfer during pregnancy.[34] Early miscarriages and fetal malformations were also detected in pregnant mice 10 days after SWCNTs injection, and teratogenicity was observed at a dosage as low as 100 ng/mouse.[35] Additionally, intragastric administration of ENPs to lactating mothers can affect CNS development of offspring, which was shown in rats orally exposed to TiO_2-NPs during lactation from day 2 post-delivery to 21 days.[92] However, the current literature on ENPs exposure in developing animals has limitations in analytical methodology that stem from deficiencies in selectivity, sensitivity, or both, and these have obscured

researchers' complete understanding of fetal exposure to ENPs. Thus, it is important to systematically assess potential reproductive and developmental toxicities of common ENPs in model organisms.

Conclusions and recommendations

Health risk assessment remarks

As new technology and innovation emerge, pros and cons need to be carefully analyzed, especially the use of ENPs. ENPs are of considerable importance, because global businesses and companies continue to invest heavily in nanotechnology for a wide range of nanoproducts. Although certain ENPs have great promise in the treatment of pediatric diseases and the development of potent nanomedicine and nanovaccines for young children, we need to ensure there are no hidden dangers in the applications. As highlighted above, our knowledge about actual ENPs exposure and nanotoxicity in infants and children largely remains unknown, and many unsolved questions remain (Fig. 3). Specifically, 1) what size(s), type(s), and degree(s) are ENPs released from consumer products or contained in nanofoods? 2) how much of a certain ENP a child may be exposed to via normal or recommended use of nanoproducts or consumption of nanofoods? 3) are there any exposure scenarios for infants and children that must be deemed as particularly critical? 4) how and to what degree(s) do ENPs cause health hazards to infants and children? Are they different from adults in response to ENPs? 5) what are the most critical or sensitive periods during development when exposure to ENPs can induce adverse effects in infants and children? 6) are there any differences in toxic effects between prenatal and postnatal exposure to a certain ENP?

It is indispensable to utilize state-of-the-art approaches that combine environmental risk assessment and biologic monitoring with the exposure patterns and developmental stages of children. Because of the aggregation or degradation of ENPs in the environment, they are no longer at the nanosized level. As some health effects of ENP exposure might not be apparent for decades, long-term studies investigating ENP safety are crucial. It will be particularly important to conduct these toxicity-testing studies with ENPs that are more widely used due to their various sizes, shapes, and surface chemistry. In addition, comparative studies to explore the toxicity differences of ENPs among different life stages are essential to help infer the health risks to children and assist with regulations and policies for ENPs.

Regulation perspectives

To date, the nanotechnology industry has generally not been regulated. Manufacturers are not required to report the use of ENPs except for SWNTs and multi-walled NTs, or label products containing ENPs,[3] giving regulatory and legislative agencies limited authority to access ENP-containing product information for exposure assessments.[4] There should be greater disclosure on what types and how many ENPs are in products and foods, and manufacturers should improve their processes to minimize potential dangers of ENPs in their products in consideration of the increased vulnerability of children and the precautionary principle. Moreover, companies engaged in nanotechnology research and development program, as well as government agencies such as the Food and Drug Administration and Environmental Protection Agency should ensure products and foods containing ENPs be safety tested and labeled for consumers. With increasing awareness of environmental exposures and detrimental effects of ENPs, newly prudent policies, laws, and guidelines for nanotechnology-related innovation must be designed and implemented as soon as possible to protect and improve human health, safety, and the environment. This research can ensure public confidence in the safety of nanotechnology research, manufacturing, and application.

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