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Micro- and nanoplastic transfer, accumulation, and toxicity in humans

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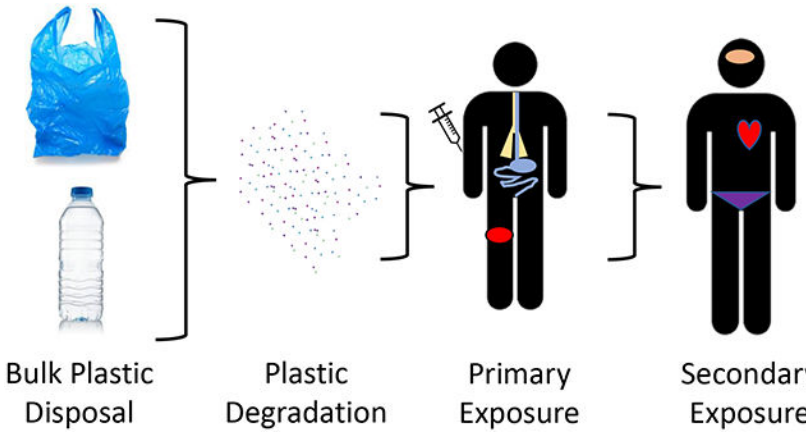
Abstract

Plastics impact our daily lives. Unfortunately, it is the disuse and disposal of these items that may affect us the greatest. Plastic micro- and nanosized particles, likely from bulk degradation, have been identified in air pollution and water sources. Recently, plastic particles have also been identified in consumable products. The purpose of this review is to identify the likely routes of human exposure, the toxicological outcomes and concerns currently reported, and to provide some considerations for future assessments.

Graphical Abstract



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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Keywords

microplastic; nanoplastic; toxicity; exposure

Introduction

The production of synthetic polymers over the last half century has been astronomical. This production, subsequent use and disposal, has directly led to an increase in plastic waste. Reports have indicated that 50% of plastic products are single-use items [1]. It is commonly acknowledged that plastic pollution is a growing environmental concern. Once discarded, bulk plastics will break down to smaller pieces identified as micro- and nanosized plastic (MNP) particles [2]. These tiny microsized particles (< 5 mm) will continue to degrade to billions of smaller nanoplastic particles (<1 μm or <100 nm, depending on the source). At these size ranges, plastic particulate can become airborne where it may be inhaled or deposited miles down wind, entering waterways and the food chain. Microplastic particles have been identified in soil samples, fresh water, aquatic animals, atmospheric fallout, and arctic snow [3]. Furthermore, the expansive industrial use of plastic mingled with the increased processing of many consumable products, has led to the identification of microplastic particles in bottled water and food stuffs [4-6]. A natural step in the understanding the of plastic particle pollution is how these particles may affect human health.

Micro- and Nanoplastic Exposure Routes

Human exposures occur through environmental interaction with the epithelial layers of the lungs, gastrointestinal tract, and skin. On rare occasions, particle-cellular interactions may occur through intentional plastic exposures. Therefore, evidence of MNP in the air, food or beverages, personal care products, or implanted devices would identify plausible human exposure routes including inhalation, ingestion, dermal, and implantation (Figure 1).

Inhalation

Microplastic particles have been identified and quantified in outdoor both and indoor air. The sources of aerosolized plastic particles include synthetic textiles (e.g., carpeting, furnishings, and clothing), roadway tire erosion and debris, and particle resuspension from waste, landfills, and emissions [7]. Wind transfer has been identified as a potential source for alpine and Antarctic plastic particles within snow samples and is estimated to contribute 7% of ocean contamination [8-10]. Plastic microfibers have been identified in atmospheric fallout, quantified as an average concentration of 0.9 m^3 110 particles/m^2 per day in Paris, ranging from 2.1-355.4 microplastic fibers/m^2 per day, and making up approximately 29% of all outdoor aerosolized fibers [11]. The variability of these values is attributed to rainfall during sampling.

While outdoor environmental exposures are of concern, greater reports of plastic particle concentrations have been identified in indoor air [12]. Indoor air measures have reported deposition rates of 1,600-11,000 microplastic fibers/m^2 per day, depending on the indoor

environment (e.g., home or office) and lifestyle (e.g., tumble dryer vs. air dry clothing, air filtration of heating/cooling units) [12]. This is especially concerning given that humans spend an estimated 70-90% of their time indoors [13].

Inhalation of plastic particles allows for nasal and pulmonary deposition based on human anatomy and particle characteristics. As with other micro- and nanosized particles, smaller and lower density particles will be more likely to reach the lower airways and alveolar regions of the lung; whereas larger particles may be cleared through the mucociliary escalator [7,14]. Plastic fibers may be especially difficult to remove from the pulmonary system, due to their high surface area and high potential of penetration [15]. Pauly et al. [16] identified microplastic fibers, defined as a diameter ≥ 3 μm and a length of ≥ 5 μm, in 83% of the 81 non-neoplastic human lung samples analyzed. Interestingly, microplastic fibers were identified in 97% of the malignant samples evaluated. These microplastic fibers were not limited to specific pulmonary regions, but found to distribute throughout the lungs [16].

Occupational studies of synthetic textile workers can illustrate the possible human pulmonary consequences associated with MNP inhalation. One well-documented outcome is identified as “Flock’s disease” or flock worker’s lung, an interstitial lung disease caused by exposure to small plastic fibers (i.e., nylon, polyester, polyethylene, or polypropylene) as they are applied to an adhesive coating to produce velvet or fleece fabrics [17-19]. Overall, workers in this field carry an increased cancer incidence correlated with concentration and years of exposure [19]. This increased cancer risk is likely associated with chronic pulmonary inflammation and oxidative stress due to local particle deposition [7].

Laboratory recapitulation of flock exposure in rats has yielded conflicting reports wherein a single intratracheal instillation exposure revealed significant pulmonary inflammation [20]; yet a four-week nose-only inhalation studies demonstrated rapid clearance with no pulmonary effects [21]. Recent laboratory studies identified more pronounced effects at the local molecular level in the expression of inflammatory proteins in lung tissues after 14 days of MNP inhalation [22]. While these studies provide an initial foray into the inhalation toxicology of MNP particle inhalation there is much work that remains.

Ingestion

Environmental contamination and particle precipitation have been identified as likely sources of MNP in consumable products [23]. This connection was originally theorized as a risk through the consumption of marine and aquatic organisms which had ingested plastic particles and subsequent migration through the food chain [24,25]. It is now evident that processing and plastic packaging play a significant role in MNP particle migration into food products [5,6]. These products include less processed sources including salt, honey, rice, and granulated sugar, as well as highly processed canned goods [26-29]. As it pertains to beverages, MNP have been identified in tap and bottled water, beer, wine, and bagged tea [4,27,30-32]. Interestingly, bagged tea held the highest yields, estimating one would consume 14.7 billion MNP particles in a single cup of tea [31]. Cox et. al [5] reported through literature review that tap water contains 4 microparticles/L and bottled water contains 94 microparticles/L. This indicates that the source and pre-processing of an

individual's drinking water (i.e., bottled vs tap water) will impact MNP particle consumption dramatically. The range of microplastics reported in bottled water is very wide, fluctuating from 0.33 particles/L [33] to 325.33 particles/L [4]; these variations may be attributed to the size detection limits of the methodologies. While it is important to recognize that MNP particle are entering human mouths, it is equally as important to note that microplastic particles are also being excreted in human stool [34]. Therefore, analyses of consumable food and liquid sources of MNP exposures are ongoing.

Most studies have been completed using polystyrene particles to assess intestinal impairment and toxicity. *In vitro* models of gastrointestinal particle exposure demonstrate nanoplastic particle (40-90 nm) uptake by Caco-2 epithelial cells and capability to cross the intestinal barrier [35]. The use of pristine and fluorescent nanopolystyrene particles in these cellular studies indicate no digestive barrier impairments or epithelial cellular toxicity [35,36]. However, functionalization of the particle through carboxylation (−COOH) or amino groups ($-NH_2$) permitted disruption of intestinal barrier function, easier epithelial uptake through endocytosis, and toxicity as identified by cellular autophagic death [37]. Furthermore, mixtures of polystyrene nanoparticles with other environmental pollutants, such as metals, markedly increases cellular uptake and toxicity [36].

In vivo models demonstrate a shift in intestinal oxidative and inflammatory balance due to direct epithelial-particle interactions; thus disrupting the gut microbiota, immune cell toxicity, nutritional uptake and impairing intestinal functions [38]. These models also echo the capability of nanopolystyrene absorption within and migration from the digestive system after oral exposure [37,39].

Dermal and Implanted Devices

While skin exposure to MNP particles is likely through personal care products and exposure to aerosolized particles. It is notable that plastic microbeads products were recently banned after disposal led to environmental contamination and accumulation. While it is unlikely that MNP will pass the healthy dermal barrier [40,41]; if the skin is damaged by small tears or sunburn, plastic particle penetration may occur. Furthermore, the mechanical wear of medical devices implanted into the human body (e.g. polyethylene articulating spacer in shoulder, knee, or hip replacement, dental implants and caps, and cosmetic implants) has been shown to allow for MNP particle production and translocation within the system [42-45].

Particle Uptake and Translocation

Micro- and nanoparticle translocation from the primary site of exposure has been a theory of how particle exposure can modulate toxicity and impact distant systems (Figure 1). Particle migration has been identified after gastric or pulmonary exposure to metallic and carbonaceous nano-sized materials [46]. Early work focused on MNP also indicate the propensity for MNP translocation and deposition.

Particle Translocation, Deposition, and Accumulation

Particle translocation from the primary site of exposure (i.e., gastric or pulmonary system) have been reported. Interestingly, intestinal disruption and increased cellular permeability was reported to be more severe after heterogeneous polystyrene oral exposure, where mice were exposed to both micro- (500 nm) and nanosized (50 nm) particles, allowed for greater intestinal accumulation and biodistribution [39]. Particle accumulation was reported in distant organs including the spleen, lung, kidney, brain, and reproductive system [37,39]. *In vitro* assays demonstrate nanopolystyrene particles can cross the alveolar epithelial barrier, an outcome influenced by particle physicochemical properties (i.e., size, density, and charge) [47]. We have identified nanopolystyrene accumulation in the maternal heart and spleen and fetal placenta, liver, lungs, heart, kidney, and brain after maternal pulmonary exposure, suggesting systemic translocation after pulmonary exposure in late-stage pregnancy [48]. These studies provide evidence of MNP migration and deposition, indicating that MNP toxicities may not be limited to the site of initial exposure. These outcomes coincide with concerns regarding cellular toxicity as evidenced by increased inflammatory and apoptotic markers [39]. Furthermore, how or if these plastics particles are removed from the system is unclear.

Secondary Exposure

Micro- and nanoplastic translocation and systemic deposition can lead to direct cell-cell interactions in the local environment. Studies pertaining to metallic and carbonaceous nanoparticles have identified secondary outcomes in the neurological, reproductive, immune, cardiovascular systems and their local cytotoxic outcomes (Figure 1). Few targeted MNP studies have been completed to date.

Neurological

Due to the capability of MNP particle translocation from the original site of exposure, there is the potential for neurotoxicity [49]. Initial studies evaluating this connection identify reduced neurotransmitter activity and neurotoxic effects with micro- and nanopolystyrene exposure [50]. Behavioral alterations in locomotion are reported in lower-level animal models but have not yet been replicated in mammalian studies [49,51]. However, more recent evidence has identified cognitive impairments in murine new-object recognition tests after nanopolystyrene IP injection exposure [51]. Interestingly, when the nanopolystyrene particles were mixed with zinc oxide nanoparticles, the cognitive impairment absolved [51].

Reproductive

The reproductive system is also impacted by MNP particle translocation and deposition. Micro- and nanopolystyrene particles have migrated to the testes, ovaries, and placenta from the original site of exposure [37,48,52]. An et al. identified that micropolystyrene uptake to the ovary reduced follicular growth and induced oxidative stress, thus promoting ovarian fibrosis [52]. Long term exposure was found to promote chromosomal abnormalities in oocytes and germ cell apoptosis, leading to transgenerational reproductive decline in *C. elegans* [53,54]. Lastly, nanopolystyrene translocation to the fetal compartment and

fetal tissues may permit nanoplastic particle deposition in progeny, local cytotoxicity, and promote the development of disease within the offspring [48].

The placenta is thought to act as a barrier between maternal and fetal system, essentially to protect the fetus from the maternal environment while simultaneously providing nutrition and removing waste. Using an isolated *ex vivo* perfusion technique, Grafmueller et al. [55] demonstrated the bidirectional transfer of MNP particles within the human placenta. Recently, microplastic particles were identified using Raman microspectoscopy within samples of discarded human placenta after real-world exposure during pregnancy [56]. While it was unclear if these particles entered the maternal system through ingestion or inhalation routes; however, this study clearly demonstrates the capability of human exposure and systemic bioaccumulation.

Immune, Cytotoxicity, and Other Systems

Cellular-particle interactions occur at the local site of exposure and after systemic translocation and deposition. Many studies have identified modified gene expression, decreased cell proliferation rates, altered metabolism, increased proinflammatory cytokines, and oxidative stress production in hematological cells, human gastric epithelium, and lymphocytes after polystyrene exposure [57-61]. *In vitro* studies of particle interactions with immune cells resulted in increased oxidative stress and impaired lysosomes in RAW 264.7 macrophages [62]. Furthermore, *in vivo* studies have demonstrated cardiotoxicity induced by oxidative stress, resulting in cardiomyocyte apoptosis and structural damage to the myocardium [63,64].

Understanding the cellular internalization of MNP particles is paramount to discern their cytotoxicity [57,65]. Liu et al. [65] identified that micro- and nanosized polystyrene particles are endocytosed through differing pathways; where microplastics were often taken up through micropinocytosis and nanoparticles were endocytosed via clathrin and caveolae-mediated pathways [65]. We should keep in mind that there is significant selection variability associated with “representative” cell lines and plastic particles utilized within these initial studies [59]. Functionalized groups, metals, organics or other proteins on the surface of the plastic producing an eco-corona can also dramatically impact particle uptake, internalization, and release [65] [62,66-68].

Considerations—While it is clear that human exposures to MNP are inevitable and early toxicity studies are underway, there are clear elements of MNP to consider in future studies (Figure 2). The material properties and particle standards, real-world concentrations in indoor/outdoor environments, bioaccumulation, and the transportation and release of adsorbed surface coating or embedded chemicals to a biological environment must all be considered.

Material Properties

One area that remains under debate when assessing human risk is the size of the particles examined. Microplastic particles are described as those less than 5 mm in one dimension. Nanoplastics, however, have been described in environmental literature as less than 1

μm (1000 nm) and in laboratory studies as less than 0.1 μm (100 nm) [69]. Currently, most assessments of environmental or consumable products cannot report nanoplastic concentrations at either definition due filter pore limitations. These have been reported as low as of 125 μm for environmental studies [70] and 11 μm for consumable products [27]. Openings of this size would allow the passage on nanosized plastics, thus eliminating these particles from assessment and quantification. While nanoplastics would fall under the greater "microplastic" umbrella, and it is tempting to ignore these delineations, classifying these terms and size ranges is crucial for biological assessments. Particles within these micro- and nano-size ranges have significantly different biological interactions and physiochemical behaviors, thus greatly impacting cellular uptake, biodistribution, accumulation, and cytotoxicity [69,71].

Chemical construct, particle shape, and surface charge may also play a role in cellular interaction, uptake, translocation, and toxicity. There are numerous polymeric compounds that may be described as "plastics". Each chemical transition between these composites begets a new toxicological profile. For example, polystyrene, nylon, polyethylene, and polypropylene particles may all behave differently in a biological environment. Furthermore, particle shape may also impact cellular interaction. Fibrous particles may lead to frustrated phagocytosis, thus increasing localized oxidative stress and inflammation, whereas spherical particles are easily internalized. Surface charge has also been shown to affect particle uptake and the binding of surface proteins in environmental or biological conditions. Given these properties, it is crucial that studies continue to characterize the MNP identified in environmental contamination and laboratory exposures.

Concentrations

Currently, there is a gap in the literature identifying the MNP particle concentrations in indoor and outdoor air, water, and consumable products. Recently a number of well-organized reviews have been published regarding MNP particle exposure, biological outcomes, and predicted human health consequences [3,7,57,68,72,73]; however, most laboratory exposures are not analogous to human toxicity studies. These studies utilize short duration, high concentration exposures while most humans are chronically exposed to low levels. Unfortunately, the real-world exposure paradigm of plastic particulate concentration and size ranges for humans in indoor or outdoor settings and urban or rural environments has not yet been established [74]. While literature reviews provide the basis for human exposure estimates [5], there is a lack of validated methods for collection, reference materials, and standardized analytical sampling and assessment techniques [57,72]. Furthermore, identifying the dosing concentrations of nanoplastic particles remains outside of our collective capabilities. Therefore, these experimental models provide a baseline start for which to build future studies. Until the environmental concentrations and doses are confirmed, the separation between laboratory exposures and real-world conditions will remain.

Bioaccumulation

Understanding MNP particle uptake, translocation, and bioaccumulation remains a barrier to human toxicology assessments. Few groups are applying imaging and microscopy

approaches to visualize particle migration from the original site of exposure. Increasing the sensitivity of positron emission tomography (PET) to assess *in vivo* pharmacokinetic behavior of MNP particles will be crucial to aid in our understanding of human toxicology [75]. The expansion of Raman and darkfield microscopy techniques will also aid in the identification of nanoplastic intracellular uptake and tissue deposition [48,76].

Toxicological Vector

It is important to keep in mind that suspended MNP particles are within the heterogenous mixture [69]. Real-world exposures to these particles are not taking place in a pristine vacuum, but instead in a conglomerate mixture of carbonaceous, metallic, biological materials, and other plastics. It has been hypothesized that MNP particles may act as a toxicological vector for the transfer of heavy metals, volatile chemicals, or biological contaminants [3,77]. Furthermore, plastics are developed with a variety of chemical additives or extrudation processing to produce specific commercial characteristics (i.e., the difference between polystyrene foam and hard solids). These “plasticizers” may not be covalently bound to the polymer, thus capable of leaching from the plastic material [69]. Much work has been done on the health effects of these chemicals leaching from the plastic product into consumable products (i.e., bisphenol A, phthalates, nonylphenols, and perfluorooctanoic acid) or being released as volatile organic compounds (VOCs) [3]. Outcomes of these toxicological assessments identify carcinogenic compounds and endocrine disruption leading to metabolic, reproductive, and developmental effects [57,73]. It remains unclear if bioaccumulation of MNP particles would permit continued local release of these chemical additives at the site of deposition.

Conclusions

Human exposure to MNP is occurring; however, the toxicological consequences of these exposures in unclear. Laboratory studies are underway to assess the routes of exposure, particle uptake mechanisms, and secondary cytotoxicities. Gleaning an understanding of real-world exposure concentrations and primary particle chemistry is paramount. Until these exposure characteristics are revealed, selection variability, as it pertains to laboratory model and particle properties (i.e., size, material, shape, functionalization groups, particle corona) will continue to persist, clouding valuable experimental outcomes and delaying regulatory action [72]. This variability extends to the differentiation between pristine particles, functionalized groups, environmental contaminants, chemical additives, and biological corona, each having a distinct toxicological outcome. Given the capabilities for particle uptake from the primary exposure site, additional studies will need to focus on the toxicities at the initial site, secondary systemic signaling, and local secondary perturbations associated with deposition and bioaccumulation. Studies in these areas may permit for the identification of exposure biomarkers [74].

Overall, domestic and commercial plastic utilization continues to rise. Therefore, plastic disposal and subsequent particle pollution remains a worldwide concern. Human exposures via inhalation and ingestion have been documented, yet the toxicological considerations of these exposures remain elusive. Focused studies to determine environmental concentrations,

human exposure dosage, particle physiochemical properties (i.e., material, size, shape, charge, and surface chemistry), mechanisms of cellular uptake, and *in vivo* outcomes are vital to determine human risk.

CONFLICT OF INTEREST AND ACKNOWLEDGEMENTS

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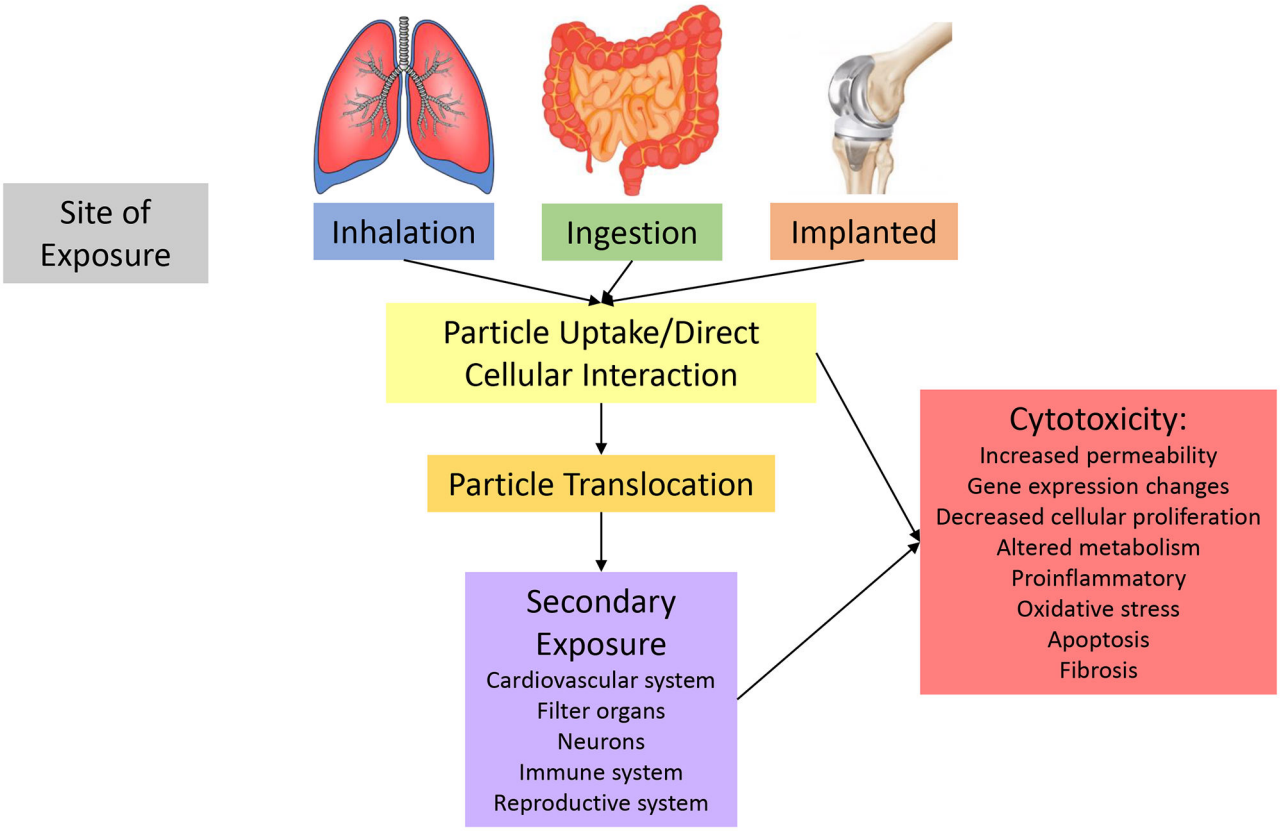

Figure 1:
Potential Fates of micro- and nanoplastic particles.

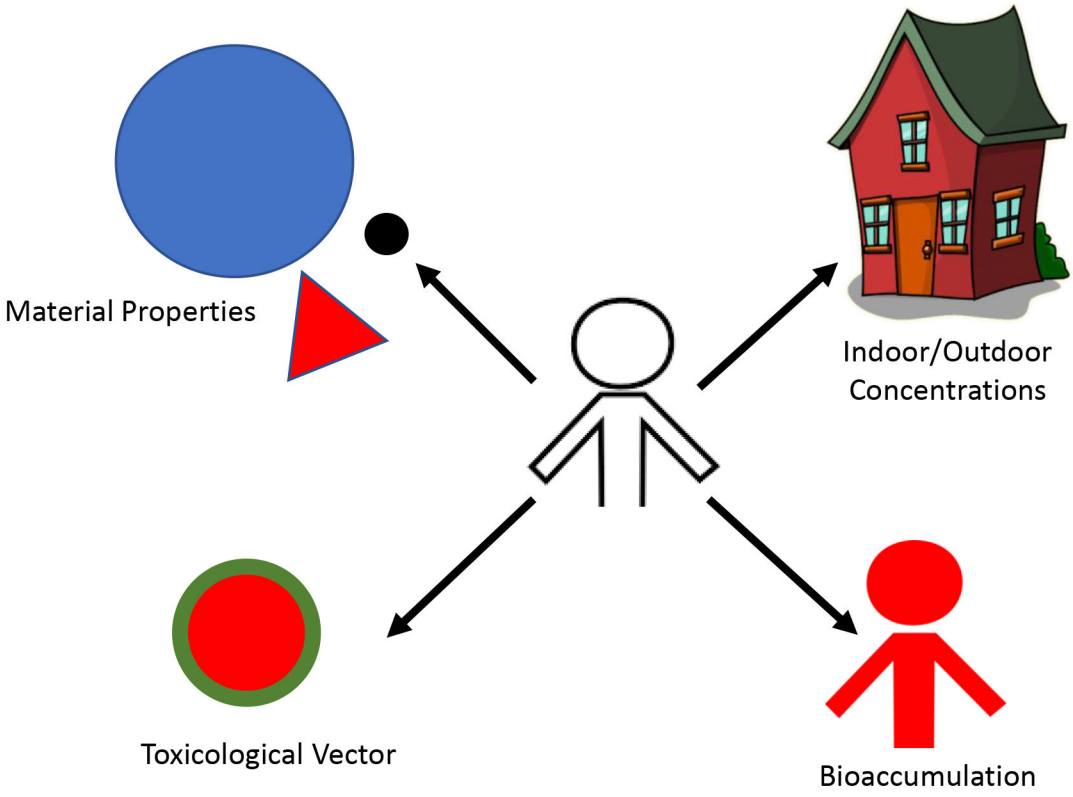

Figure 2:
Considerations for future assessments.