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A Review of Data for Quantifying Human Exposures to Micro and Nanoplastics and Potential Health Risks

Gregory M. Zarus[1], **Custodio Muianga**[1], **Candis Hunter**[2], **R. Steven Pappas**[2]

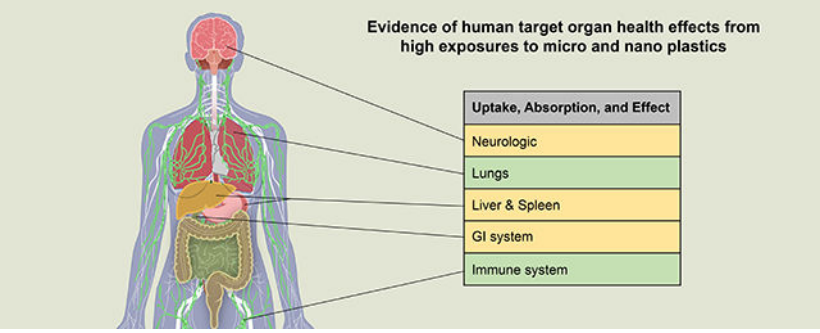
[1]Agency for Toxic Substances and Disease Registry, 4770 Buford Highway, Atlanta, GA 30341, USA

[2]National Center for Environmental Health, 4770 Buford Highway, Atlanta, GA 30341, USA

Abstract

Plastic debris have been shown to degenerate to particle sizes that can be transported in air, water, and food. Small particles are documented to enter and exit our bodies and translocate to and from some internal organs. Health effects on respiratory, hepatic, immune, and gastrointestinal systems have been reported in humans and other mammals in response to elevated particle or fiber exposures. These health effects differed by plastic type and size, and there was evidence of dose response for a few health endpoints. We conducted a systematic word search and reviewed published literature to identify microplastic and nanoplastic studies that quantified exposure via the ingestion, inhalation, and subcutaneous absorption (not dermal) exposure pathways; identified translocation, internal dose, and associations with health effects and markers related to exposures to specific sizes and types of plastics. We identified the data gaps in relating exposure data to health effects and biomarkers, most notably the lack of characterization of plastic particles and fibers smaller than 10 microns in most media.

Graphical Abstarct



Keywords

microplastics; nanoplastics; environmental exposures; biomarkers; health effects

Disclaimer

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Introduction

Microplastics (MPs) are plastic particles with a size less than 5 millimeters (mm) that pervade the environment because of extensive plastic use and persistence of the polymer materials (Frias & Nash, 2019). Nanoplastics (NPs) have been defined as plastic material less than 0.001 mm (1 μm, da Costa et al, 2016). Because of many beneficial characteristics, MPs and NPs have been intentionally placed in cleaning products, coatings, cosmetics, and medical applications (Thompson, 2018; AMEC, 2017; Leslie, 2014) and are also created when bottles, clothing, tires, and packaging break down in the environment. From those sources, MPs and NPs can be transported into streams and seas, carried into the air, and fall with rain (Cai et al., 2017; Underwood et al., 2017). They can be ingested by marine animals and be found in fish, crabmeat, and table salt (Waite et al., 2019; Yang et al., 2015). As with other persistent organic pollutants, the primary MP and NP exposure routes for humans are suspected to be inhalation, ingestion and dermal absorption, with evidence confirming inhalation and ingestion. MP and NP markers have been detected in urine and feces (CDC, 2019; Schwabl et al., 2019). Since MP and NP markers have been detected in human waste, health scientists must investigate whether absorption occurs and whether exposures to MPs and NPs are harmful.

Recent news of large plastic debris physically harming the internal organs of whales and birds raises pertinent questions about which types of plastic are potentially bioactive in people and may be harmful to human health. People can avoid swallowing large plastic debris, but perhaps the less avoidable smaller plastics debris could pose physical or physio-chemical harm to internal human systems. The Agency for Toxic Substances and Disease Registry (ATSDR), with its long history of evaluating community exposures, is joining the National Center for Environmental Heath (NCEH), with its experience in evaluating national exposure trends, to investigate literature involving human exposure to MPs (NCEH/ATSDR, 2019). This review of the literature summarizes the evidence of exposure, the largest data gaps in quantifying exposure, and the potential for microplastic substances to pose a public health hazard. The evidence includes:

1. MP data collected in food and water that allow us to calculate some exposures;
2. Worker and animal exposure studies that show the unique toxicity of different MPs;
3. Biomonitoring data that indicates markers of exposure and effect that suggests physio-chemical effects.

Review Methods:

We conducted three initial internet searches for all published articles and followed up on categorical searches for each, namely:

1. **Human environmental exposure:** We included the specific terms for, “microplastic” and “environment” and identified those published articles that that indicated human exposure through ingestion or direct inhalation, exposures included in ATSDRs exposure guidance (2016 a,b,c, & 2018). We also reviewed

references for additional publications. We requested raw data from some authors to calculate potential human exposures.

2. **Worker Exposures:** We conducted specific searches for worker and occupational exposures to synthetics, textiles, flocking, polyvinyl chloride, PVC, nylon, polyethylene, plastics, and aramid. We also reviewed references for additional publications. We then used search terms listed in the referenced animal studies.

3. **Biomarkers of exposure and effects**: We conducted specific searches for biomarkers of exposure to both plastics and synthetics. We followed up with searches on those references and included additional terms for implant degradation.

More than three hundred articles were identified from the initial searches. Articles were divided into folders in a federal share site (Max.gov\HHS\Microplastics). The list of the fifteen initial folders included in the share site are as follows: air, analytical methods, biota, citizen science, freshwater, human, human epidemiological case studies, human food, ice and polar regions, saltwater, sediment, soil, wastewater, worldwide distribution and transport. Additional publicly available data were screened and added as discovered, in a less systematic way, during the development of this manuscript. During the review process of the manuscript, references were added to describe specific processes.

Human exposure to MPs in the environment

Worldwide, MP ingestion has been recorded in about 200 animal species (Wang et al., 2016; Wang et al., 2018). However, researchers have examined only a few of the sizes and types of polymers that are characteristic of environmental MPs and only a handful of the MP-containing media to which humans are exposed (Dris et al., 2017; Kosuth et al., 2018; Leslie, 2014). Most MP studies focus on ecological effects rather than human health effects. Many of those ecological studies are conducted with a species-specific focus to determine if the MP is affecting them. (Underwood et al., 2017). Thus, it difficult to relate the exposures up the food web (Koelmans, 2020). Furthermore, the sampling methods differ widely from those used to measure synthetic fiber or other plastic microparticles within highly exposed people (Zarus, 2020). Therefore, it is difficult to make direct comparisons of many studies. Calculating a dose for human exposure to MPs requires data on their polymer types, sizes, masses, and numbers in food, water, or air. However, studies addressing human exposure have not yet provided these data, and only a handful of environmental studies have the appropriate data to quantify human MP exposure (Table 1).

Humans come into contact with MPs through inhalation, ingestion, and dermal absorption routes (Dris et al., 2017; Kosuth, Mason, & Wattenberg, 2018; Leslie, 2014). Bivalves (clams, mussels, or oysters) are commonly examined as quantitative aquatic exposure models because they filter MPs from the water and accumulate them easily. Some of the data collected on these species can be related to calculate human exposure. To relate these data to human dosimetry, ecologists and environmental scientists weigh the edible flesh and report

the MP counts per unit tissue mass (Li et al., 2016; Su et al., 2018; Van Cauwenberghe & Janssen, 2014; Waite et al., 2018).

Although we can calculate doses from these studies, each study focuses on MPs of different sizes, and none focus on very small (<25 μm) particles that may be absorbed by people who eat bivalves. Different MP size ranges, including smaller particles to which humans may be exposed have been studied in soil, fertilizer, and plastic tea bags (Esan, Abbey & Yurgel, 2019; Weithmann et al., 2018; Blasing & Amelung, 2018).

Although the data from these studies represent only a small portion of our total potential MP exposure, they demonstrate that humans are exposed to MP particles of sizes and compositions for which studies reviewed in this manuscript have demonstrated health effects. Effects include tissue lodging of MP in spleen and liver and tissue immune response associated with degradation of plastic implants; and lung damage from inhalation, and associations with liver and gastro intestinal effects from workplace exposures (Walker & Bullough, 1973; Vobecky, Devroede, & Caro, 1984; Hicks et al., 1996; Burkhart et al., 1999; Urban et al., 2000; Ward et al., 2002; Nichols et al., 2013; Gennaro et al., 2008). Table 1 summarizes several studies of the environmental media through which humans may be exposed and attempts to estimate a daily MP dose for these media. These doses are calculated using established exposure factors or average intake rates per person where appropriate (ATSDR 2005; ATSDR 2016 a&b; ATSDR 2018; HHS 2015), without dividing by the many possible body weights that represent specific U.S. populations (ATSDR 2016c). The established exposure factors allow direct estimates of exposure within Table 4. An inhalation rate of 15 M^3 per day can be applied to the 5.4MP /m^3 to estimate a daily exposure of 81 MP and a water consumption rate of 3 L per day can be applied to the tap water measurement of 9.24/L to estimate a daily exposure of 28 MP.

Other calculations require a few steps. A typical fish consumption rate of 8 ounces per day can be directly applied to the average mass of the fish reported by Karami et al., 2017. In that study, scientists identified 61 MP-like particles were isolated from four small fish species (n= 30 each) totaling approximately 761g. The species ranged from anchovy to Indian mackerel (ranging 1.5–58.5 g), with an average fish mass of 25 g. Thus, there are 2 MP for each 25 g of fish and 18 MP for each 8 ounces (or 227 g) of fish. Recognizing that wet weight is often more representative of what people eat (ATSDR 2005), the MP wet concentration could be 10% of the dry weight, resulting in a low estimate of 2 MP/ 8-ounce fish. This particular fish study provided additional characterization, as they reported frequency distributions for each species and provided data on fragments, film, and filaments. This could allow for more specific exposure assessment for these fish. This information is not comparable to most other studies.

While a general MP inhalation dose can be calculated from one set of environmental studies (14–81/day) (Dris et al., 2017; Gasperi et al., 2015), there were several data gaps that preclude any health assessment of human exposures. The fibers collected were larger than 50 μm limiting evaluation of possible effects observed in highly exposed populations (Zarus, 2020). Although many studies calculate doses from food sources like clams, mussels, and oysters, these sources make up a small percentage of U.S. food consumption. A single 8oz

serving of oysters and clams might expose humans to 2000 MP particles, but nothing is known of MP exposure from the more common U.S. diet, consisting of chicken, pork, beef, wheat, and vegetables. Although most studies focus on the gastrointestinal tract of fish (Rochman et al., 2015; Karami et al., 2017), there are some data to evaluate human MP uptake from fish. Scientific literature suggests we have exposure of 2–10 MP particles per fish we eat (Karami et al., 2017). Marine studies also find MPs in plankton, but not the plankton typically consumed by people directly and indirectly (Baini et al., 2017). However, we know that humans consume an algae-derived tablet for osteoarthritis, which by the study-inference would contain 2 MP particles, and humans also ingest Nori wraps (for Japanese foods), which by study-inference, could contain 113 MP particles.

U.S. residents typically consume meat from livestock and poultry more frequently than fish and shellfish, but no MP studies are currently available for those meat sources. However, data are available for sea clam viscera, which is a good protein (lysine) supplement for growing pigs and clams readily accumulate MPs (Wohlt et al., 1994). A pig eating 2 kg/day with less than 5% clam viscera could by inference ingest 200 MP particles/day –18,000 particles in 90 days (from clams with 2 particles/g). Additional MP exposure to pigs is possible from ingesting the MPs found in soils (Blasing & Amelung, 2018). Drawing from other animal and cell exposure studies, some of these plastics are excreted, but there is evidence of some accumulation (Underwood et al., 2017; Watson et al., 2016).

Several studies have demonstrated large quantities of MPs in table salt and suggest that sea salt has even larger quantities (Iñiguez, Conesa, & Fullana, 2017; Kosuth et al., 2018; Yang et al., 2015). Typical use of salt in the United States could result in human ingestion of 4 MP particles/day (HHS, 2015). Although fewer data are available on drinking water, the limited data suggest consumption of 4–30 MP particles about 1 mm in length per day in water; however, fine particle concentration is unknown (Kosuth et al., 2018). Analysis of tea from tea bags, however (Hernandez et al., 2019), revealed that tea drinkers ingest billions of NP particles from a plastic tea bag. Adding a teaspoon of sugar could add about one MP particle. Although the tea analysis included MPs 50 times smaller than those measured in water (and sugar), no clear method is available to calculate cumulative MP doses.

Despite the focus on ecological studies of marine environments, little is known about marine exposures for subsistent populations. MP calculations from a diet of bivalves and some fish suggest that human MP ingestion among sea-subsistent populations would result in exposure to 1,000–5,000 MPs/day; however, the full diet of these populations is not well known. A recent study of whales found 8,000 – 29,156 ng/g phthalate esters (PAE) in whale blubber (Baini et al., 2017). A survey of Native American communities identified one community harvesting 32.6 kg of whale per person in 2005–2006 (Ahmasuk et al., 2008). Consuming one third of this amount could result in a possible ingestion dose of 31 to 114 mg/yr of PAEs. While there is no relationship between whale PAE to MPs, there are ratios in plankton and seawater. Whale PAE levels were 5 to 18 times higher than in the plankton consumed by the whales whereas other studies find just trace levels of PAEs in seawater, 3–1000 times lower than in the plankton (Heo et al., 2019; Corchran et al, 2009; Paluselli et al., 2018a, 2018b). Seawater PAE concentrations were highly correlated with seasonal re-suspension of plastics and microplastics (Paluselli et al., 2018 a, 2018 b; Xie et al. 2007).

If the same ratios of MPs to PAE were applied to whale meat, it would suggest 7–26 million MPs per year (71,000 MP fibers per day). This value is a thousand times more than the exposure from fish and clams shown in Table 1 and hundreds of times higher than calculated in recent studies (Cox et al., 2019; Senathirajah & Palanisami, 2019). Thus, the lack of MP and NP analysis in whale and other mammals is a large data gap in determining MP exposure in many, especially subsistent, populations. Absent critical data in mammals, some diets could result in ingestion rates from 50 to many thousands to many billions of microplastic fibers and particles per day (of varying sizes <5mm). This range is much broader than the ranges determined in two recent MP consumption studies of about 100–300 particles/day for ingestion and 210–330/day for ingestion and inhalation (Cox et al., 2019; Senathirajah & Palanisami, 2019), which has been described as amounting to “a credit card’s worth of microplastics” per week (WWF, 2019).

Evidence that some microplastics are harmful to people

A few dozen studies of workers, animals, and patients with plastic implants have provided evidence to suggest unique toxicity from exposure to some types of MPs (Chen et al., 2019; Zarus et al., 2020 b). Lung effects are associated with size, form, and type; liver effects were associated with type; immune effects appear to be more effected by size and shape; yet the full mechanisms of toxicity are not as well studied as other particles. Table 2 presents a summary of worker-related studies that indicate some unique health outcomes. The table summarizes the exposure measurements and health effects associated with three industries that commonly use MPs: flocking (applying surface texture), textile, and polyvinyl chloride (PVC) manufacturing. Workers within all three industries report respiratory effects associated with inhaling MP dust. These effects contrast with (different) effects associated with inhaling natural fibers. People working longer or in dustier (MP) areas had more severe health effects (Valic & Zuskin, 1977). Some studies include measurements of total dust, but not enough samples to determine a dose response, in people or in animals (Atis et al., 2005; Burkhart et al., 1999; Valic & Zuskin, 1977; Pimentel et al., 1975). The mechanisms of toxicity are much less understood compared with natural mineral particulate exposures. Early studies of mineral toxicity, such as asbestos, found that thin fibers deposited and accumulated in the lower lung at higher rates than thick fibers. Synthetic fibers were not as thin as the most harmful natural fibers. However, synthetic fibers have become much finer in the past 20 years (Warheit et al., 2001). These effects are apparent in three industries (Table 2) and a few follow-up animal studies (Marsh et al., 1994; Porter et al., 1999; Pimentel et al., 1975).

Flocking:

The main effect reported in flock workers was pulmonary inflammatory response, whether the synthetic polymer was nylon, polyethylene, or polypropylene (Burkhart et al., 1999; Barrow 2002; Atkis et al., 2002). A follow up animal study using nylon flock from Burkhart (Burkhart et al., 1999) indicates that the nylon MPs were the cause of toxicity, rather than the nylon diacyl chloride and diamine monomers (Porter et al., 1999). All lung-inflammatory endpoints increased after one acute inhalation exposure to MPs, along with fibrosis-induced lung remodeling with continued exposure to nylon particles; but no

significant inflammatory response was observed in the comparison group that was exposed to nylon monomers as a liquid. Additionally, the majority of MPs identified in industrial exposures were larger (10–15 μm) than would normally be described as respirable particles, suggesting that ingestion or dermal exposures may also have occurred (Burkhart et al., 1999). Respirable dust levels were very high in this study, 5–40 mg/m^3. All 143 valid worker pulmonary X-rays were abnormal; and all workers who worked in areas with highest dust concentrations reported recent pneumonia or asthma.

Textiles:

Studies of workers exposed to synthetic fibers and synthetic textiles reported colorectal cancer in addition to respiratory effects. Exposure to polyester antigens resulted in visible antibody precipitin reactions, but exposure to nylon, wool-polyester, or controls did not (Pimentel, Avila & Lourenço, 1975). While several studies indicated similar health effects from these fiber types, the industries are increasingly developing finer sized fibers (Warheit, et al., 2001). Aramid (i.e.; Kevlar®) worker and animal exposure data are limited, but fractured Aramid fibers have properties that deserve further study (Marsh et al., 1994; Xing & Ding 2007). One health hazard evaluation identified Aramid fiber respiratory risks similar to other synthetic textiles, but the concentrations of airborne fibers was much lower than reported in textile facilities with other polymer fibers (NIOSH 2000; Valic & Zuskin, 1977). However, protein markers indicated that Aramid MPs (of 6 × 0.4 μm) were as cytotoxic to cultured tracheal epithelial cells as crocidolite (3.14 × 0.15 μm) or chrysotile (3.21 × 0.063 μm) asbestos (Marsh et al., 1994). The response increased with dose in terms of either mass or fiber count, but calculation of an equivalent inhalation dose from cultured cells is not possible. Other animal studies indicate that Aramid could degrade in the lungs (Warheit et al. 2005) or within incubated blood cells (Wening & Lorke, 1992). However, these studies used uncoated Aramid fibers. Newer advances of coatings, with nanomaterials reduce the degradation of Aramid fragments (Xing & Ding 2007).

PVC:

Studies show a clear difference between PVC and other synthetics. PVC MP workers were found to have elevated incidence of lung and liver cancers, but no colorectal cancers, in contrast with the elevated incidence of colorectal cancers observed among those who worked with other polymers used in textiles, but there are insufficient details to link PVC dust to the liver cancers. A large class action among Italian vinyl chloride and PVC workers resulted in several studies to differentiate exposure types. Although the liver is a target organ of vinyl chloride vapor inhalation (ATSDR, 2006), PVC particles were thought to not affect the liver as extensively. In another study, PVC dust exposure was associated with risk of liver cancer among workers (Mastangelo et al., 2003). Those working as PVC baggers showed significant increase in deaths from all cancers and cardiovascular disease, but only the autoclave workers showed significant liver tumor-related deaths (Gennaro et al., 2008). Dust measurements and characteristics varied within these facilities. Total dust ranged from 0.15 to 18.4 mg/m^3 in some areas and 0.28 to 45.6 mg/m^3 in the workers' personal monitors with averages of 7 mg/m^3 in the suspension and 5.2 in the mg/m^3 in the emulsion areas (Casula et al., 1988). Other indications of differential toxicity are found in rodent studies showing that

PVC particles caused pulmonary inflammation and damage similar to silica-induced inflammation after 2 days (Xu et al., 2004).

Although these studies revealed toxicities that differed among MP types, the health risks were as severe as other occupational dust exposures. In comparison, carbon black manufacturing workers were exposed to primary submicron (10–500 nm) particles and their aggregates (80–800 nm) during the manufacturing process (Gardiner et al., 1992). These workers developed small opacities on chest radiographs and showed both decreased forced expiratory volume in 1 second (FEV1) and decreased forced mid-expiratory flow (FEF25–75%); they also exhibited symptoms of chronic bronchitis (Gardiner et al., 1992; 1996; 2001). In an animal model, Brown et al., 2001 demonstrated a significantly greater neutrophil influx in rat lungs after instilling 64 nm polystyrene particles compared with 202 and 535 nm particles of polystyrene. The large surface area to mass ratio observed in micro polystyrene (Brown et al., 2001) was considered the possible cause of greater pro-inflammatory activity.

Although the available worker studies do not provide sufficient information to permit calculation of a MP dose response, the measured levels of respirable MP dust were about 1000 times higher than levels measured in household air (Dris et al., 2017). Permissible worker exposure levels to dust are about 100 times higher than ambient air quality standards (ACGIH, 2019; EPA, 2014). See Table 2.

Markers of MP exposure and health effects

The reports of colorectal and liver cancers among synthetic fiber and textile workers suggest evidence of exposure by uptake and absorption of the fibers by inhalation and ingestion. Table 3 summarizes some of the evidence. In many of these cases, the evidence was not specific to just microplastics exposure, but can be used to explain transport or uptake when combined with other methods. In a recent study, MPs were found in feces of eight individuals, independent of the individuals' occupation (Schwabl et al., 2019). This suggested that the general population has some MP exposure. However, these results do not represent what was absorbed into the body. Many other studies identify phthalates alone (absent MP) which could be the result of MP exposure, phthalate only exposure, or exposure to phthalates from plastic product use (CDC, 2019).

Smaller particles, e.g., NPs, pass through cell membranes more readily. Unfortunately, few data are available on transmembrane nano-sized plastic exposure and transport. But breakdown PE plastics (MP and NP) have been identified in lymph nodes (Urban et al., 2000). Other studies revealed that nanoparticles (of 0.02–0.05) microns can diffuse through lymphatics along with fluids, proteins, immune cells, and return to the blood (Ikomi et al., 2012; Al-Sid-Cheikh et al., 2018). While scallop membranes differ from human membranes, studies also showed that scallops took up and eliminated 0.024 μm polystyrene faster than 0.25 μm particles and provided evidence that the sub-100 nm (0.024 μm particles) were translocated across membranes (Al-Sid-Cheikh et al., 2018). The hydrophobic core of the plasma membrane blocks large, polar, and charged particles, but many nanoplastics are not charged and could theoretically passively permeate cell membranes (Yang & Hinner, 2015).

Uptake of particles as large as 100 microns has been observed (Volkheimer, et al., 1962, 1969, 1975, 2001), but it is possible that some types of particles are more easily absorbed than others.

Recent studies of implanted plastic, ceramic, and other materials indicated that the shapes and sizes of the capsules affected absorption, more so than the material. Implanted capsules as large as 2 mm produced a tissue response. Capsules 1.5 mm in length caused greater effects than smaller ones, possibly due to the greater mass (Ward et al., 2002; Nichols et al., 2013; Veiseh et al., 2015; Andorko & Jewell 2017). Most of the studies of MPs in the environment report data related to particles of this size (0.1–3 mm) (Table 1).

Some health studies have reported an immune response to absorbed particles. Immune responses were clearly observed in patients whose polyethylene (PE) plastic implants were degrading (Walker, 1973; Hicks, 1996; Urban, 2000). The majority of the MP particles (PE) measured in abdominal lymph nodes were 1 μm, and the largest were 50 μm (Urban, 2000). These sizes are consistent with the size range of particles shown to be transported within the human (or mammalian) body (Volkheimer et al., 1975; Walker et al., 1973; Kononenko et al., 2015; Andorko & Jewell, 2017). Exposure to polyetheretherketone (PEEK) particles resulted in a similar immune effect (increased inflammatory cytokine release) as PE in animal studies. Approximately 13 μm PEEK particles had the greatest effect (Stratton-Powell et al., 2018). Although MP studies of patients with PE and PEEK implant breakdown focused on immune responses, other effects are possible. A report from an in-vitro study found that elevated concentrations of polystyrene (PS) NP were cytotoxic to cultured mouse neuronal cells. The cytotoxicity evident by the release of proinflammatory cytokines from the cells, however, was only detected at high particle concentrations (Jung et al. 2020). Cytotoxic effects have been seen with other nanomaterials (Kononenko et al., 2015). However, PS is less dense than water, and the cytotoxic properties required the use of culture techniques that allowed bilamellar particle exposure and accumulation of PS particles in cells (Watson et al., 2016).

Because of increased possibilities of exposures to components of plastic products, NCEH/ATSDR has been tracking plasticizers (including phthalates) found in the urine of the general population reported in the National Health and Nutrition Examination Survey (NHANES) for 2003 – 2017 (CDC, 2019). ATSDR has developed toxicological profiles addressing the health risks of several phthalates (ATSDR, 1995, 1997, 2001, 2002), including potential risks for reproductive and developmental toxicities in animals. Although no directly measured correlation exists between MP exposure and urinary phthalate metabolites, recent studies found a correlation between phthalate and MP concentrations in marine plankton and in sea water (Baini et al., 2017; Paluselli et al., 2018, 2019). Several marine researchers have identified the potential for persistent organic pollutants (POPs) and other toxicants to adsorb on micro-plastic surfaces (Prata et al., 2020; Bakir et al., 2014). Toxicants that had been adsorbed on fibers have been directly measured in occupational settings (Burkhart et al., 1999). While this research is valuable for estimating the total risk from MPs and NPs in the environment, it is not essential to determine risk from POPs. Human biomonitoring currently provides exposure data on POPs from all sources (CDC, 2013 & 2019), while the total body burden of MP and NP remains unknown. Better

assessment of MPs and NPs in the environment and directly in humans will facilitate estimating the health burden of harmful bioactive MP and NP exposure from the environment.

Research gaps and next steps

In summary, humans are frequently exposed to MPs and NPs from multiple environmental sources. Some people are exposed to thousands of plastic fibers and particles per day or more from the environment. Health effects from MP-exposure have been demonstrated in workplace studies and in patients who have had erosion-wear of plastic implants, but these exposures cannot be compared with environmental exposures. Research gaps include differences in definitions, non-standardized sampling procedures, various analytical techniques, and limited studies quantifying human exposure, uptake, dose, and effects. Table 4 identifies general data gaps in estimating human exposures (the top portion) or human uptake and absorption (on the bottom portion). It draws from the studies provided in the previous tables. The table is shaded to identify the most critical data gaps. The first row in the “Exposure Element” section of Table 4, for example, summarizes that while MP measured in air allows us to calculate a dose (provided in Table 1), that data does not include the NP concentration necessary to compare with health effects (as demonstrated in Table 2). The first row within the “Uptake and Absorption” section, identifies that lung tissue uptake is well demonstrated in workers, yet little is known in non-workers. Several analytical tools are currently available to fill many of these knowledge gaps and efforts to standardize methods are underway. By simply using worker fiber and particulate monitoring, we can measure and characterize non-worker air levels. Similar lung biopsies of deceased non-workers may provide non-worker exposure impact data. Newer methods show promise for identifying uptake and impact to critical organs or tissues. In a recent report, MP (plastic monomers) were found in human liver and fat tissue analyzed using mass spectrometry (Rolsky 2020).

To address these gaps, NCEH/ATSDR has conducted several activities to advance MP and NP exposure methodology, including contributing to multiagency sampling guidelines and assisting universities with MP and NP sample collection. To further advance the science of MP public health, NCEH/ATSDR has developed a strategic plan and committed a small group of diverse scientists to prioritize and realize strategic objectives.

The NCEH/ATSDR team’s foremost objective is to characterize potential human health risks from MP and NP exposures by conducting a scoping review of the literature. In addition, we are investigating bioaccumulation of MPs and other organic pollutants. The investigation will include systematic review analyses to inform guidance on data quality objectives for human health. Both NCEH and ATSDR have experience in this work, which includes synthesizing literature for toxicological profiles, standardizing sampling and analytical methods to monitor exposures and their health effects and tracking national trends of environmental health exposures. Building upon results of the health risk characterization, we plan to coordinate with stakeholders to drive action-based microplastics interventions to protect human health. This includes national-level activities through our established organizational cooperatives and community-level activities as we work though our site-

specific projects. Current updates are presented to the Nanotechnology Environmental and Health Implications (NEHI) Working Group under the National Nanotechnology Initiative (nano.gov.). Work is underway to develop additional outreach.

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- Humans are exposed to microplastics via ingestion, inhalation, and absorption.
- There is little exposure information on nanoplastics and most foods.
- There is evidence of uptake, absorption, translocation, and effect.
- Impacts reported on the immune, respiratory, gastro-intestinal, and hepatic systems.
- Effects and target organs are dependent on plastic type, size, and amount.

Table 1:

Microplastic concentrations and sizes found in human exposure media

Source	Concentration (in numbers)	Size (in μm)	Estimated Exposure (EE)
Fish gut. (high) (Rochman et al., 2015) *	1.6 /fish gut *	6300 × 10–2100 * >500 most	2 / gut
Fish gut(low) (Rochman et al., 2015) *	0.1 /fish gut *	6300 × 10–2100 * >500 most	0.06/gut
Fish gut(Rochman et al., 2015) *	5.9 /fish gut *	3500 × 100–4500 >500 most	12 /gut of 8oz fish
Fish (dried) (Karami et al., 2017)	2 /small fish	1–1000 Typical 100–200	2–10 /8oz
Mussels (Li et al., 2016) Clams (Yang et al., 2015) Clams (Su et al., 2017) Clams (Van Cauwenberghe & Janssen, 2014) Oysters (Van Cauwenberghe & Janssen, 2014) Oysters (Rochman et al., 2015) Oysters (Waite et al., 2018) Crabs (Waite et al., 2018)	1.5–7.6/msl **0.9–4.6/g** 4.3–57.2/clam **2.1–10.5/g** 0.4–5/clam **0.3–4.9/g** **0.47 /g** **0.36 /g** 0.6 /oyster **3.84/g** 16.5/oyster **1362/g total** **298/g tissue** 22.7/crab	17–79% <250 33–84% <250 0.021–4.83 25% <10 73% <25 5500 × 20–50 >1 QA >300 >1 >1 QA >300	9–45.6/half doz **204–1043/8 oz** 25.8–343.2/half doz **476–2381/8 oz** 2.4–30/half doz **68–1043/8 oz** **107/8 oz** **82/8 oz** 3.6 /half doz **871/8 oz** 99/half doz **308,902/8 oz** **67,586/8oz** 91/4 crabs
Seaweed (Baini et al., 2017)	22.57/sample **1.6 μg/g PAE**	<500–5000 30% 1000–2500	113/Nori wrap 1.9/OA pill 0.4 PAE mg/Nori wrap 0.007 mg PAE/OA pill
Salt (Yang et al., 2015) Salt (Iñiguez et al., 2017) Salt (Kosuth et al., 2018)	**7–681/kg** **128/kg** **212/kg**	**55% <200** **50–4300** **30–350** **10–5000**	**4 /day** **1 /day** **2 /day**
Sugar (G. Liebezeit & Liebezeit, 2013) Honey (G. Liebezeit & Liebezeit, 2013; G. L. Liebezeit, E, 2015)	**249/kg** **175/kg**	**10–3100**	**23/22 tsp** **3.7/tbsp.**
Indoor air (Dris et al., 2017) Indoor air (Gasperi et al., 2015)	**5.4 /m^3**	**50–3250** **50–80% 100– 500**	**81 /day**
Outdoor air (Dris et al., 2017)	**0.9 /m^3**	**50–1650**	**14 /day**
Tap water (Kosuth et al., 2018)	**9.24/L**	**960 average**	**28 /day**
Bottled water (Kosuth et al., 2018)	**3.57/L**	**970 average**	**4 /day**
Beer (Kosuth et al., 2018)	**4.05/L**	**990 average**	**2 /day**
Tea (Hernandez et al., 2019)	**12 ×10^9/cup** **3.5×10^9/cup**	**8.6–29.3 average (and 22–156 nm)**	**11.6 ×10^9/day** **3.5 ×10^9/day**
Soil (with compost) (Blasing & Amelung, 2018)	2.38–180/kg 1200 mg/kg	>1–5000	**<0.036/day** **<0.24 /day**
Total (fibers per day)		**Diet dependent**	**>50 -to - billions**

1. Color shading separates media groups.

2. Notes:

* Collected from gut and GI tract, not flesh. Reported as number of pieces or fibers of debris/animal for species when n>6. These studies included length and width measurements and the length of the majority of the debris observed. These do not directly apply to most human exposures.

3. **EE =** exposures were estimated by using the researchers' notes when available converting their measured concentration per sample in terms of a reasonable portion such as 8 oz fish, half dozen clams, etc. ATSDR (2016 a,b,c) exposure factors were used when applicable. The HHS (2015)

report of sodium intake of salt was used to estimate MP from salt (mole/mole) assuming the Institutes of Medicine (2004) finding of 90% dietary sodium is from salt.

4. **Bolded** data contains MP concentrations per unit mass –required for our dose calculations. QA >300 = Quality assurance with spiked samples >300μm. PAE = Phthalate esters; OA pill = common algae-derived mineral substitute for osteoarthritis sufferers (80 mg); Nori wrap (for sushi) = 2.5 g per wrap; μL = microliters

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Table 2:

Occupational exposure and hazards studies and available dust measurements

Author(s), year	Industry	Study methodology [sampling type]	Findings
(Burkhart et al., 1999)	Nylon flock	Worker questionnaire, chest X-ray, spirometry; and lung diffusing capacity tests; [RD =5–40 mg/m^3, EU, CFU]; *in vivo* toxicological studies to evaluate toxicity of the plant's dust.	Frequent respiratory or systemic symptoms significantly associated flocking ranges and performing blowdowns with number of days or hours worked/ week Toxicological studies (rats): acute inflammation
(Eschenbacher et al., 1999)	Nylon flock	Patient reports	Reduced lung volume in 13 of 20 patients; reduced lung capacity in 10 of 20 patients
(Kern et al., 1998)	Nylon Flock	Chest radiography, pulmonary function tests, computed tomography & serologic testing and bronchoalveolar lavage, lung biopsy.	Peribronchovascular interstitial lymphoid nodules in 7 patients. Nylon fiber is the suspected cause of this condition.
(Kern et al., 2000)	Flock	Lung biopsy review and questionnaire	Reduced lung volume among the 5 cases
(Barroso, et al., 2002)	Polyethylene flock	Case study of symptomatic female flock workers	Reduced lung function and reduced lung volume over 4 years.
(Atis et al., 2005)	Polypropylene flock	Case control study with respiratory questionnaire, physical examination, chest radiograph, and pulmonary function testing [TD =4.4 to <10mg/m^3, RD <0.2 to 5 mg/m^3]	Respiratory symptoms (e.g., dyspnea, cough, phlegm, wheezing, or chest tightness) increased 3.6 × in flock workers compared to controls. Serum interleukins were several times higher in flock workers (indicators of ongoing inflammation).
(Vobecky, Devroede, & Caro, 1984)	Synthetic fiber manufacturing	Case control study of colorectal cancers.	Colorectal cancers were higher in fiber drying areas: 44% of the cancer patients (n=43) worked in one of the three departments compared to 21% of the controls
(Zuskin et al., 1998)	Synthetic fiber hosiery; ventilation installed.	Cross sectional study; unmeasured polyester dust. Manufacturing process included spinning and weaving fibers and cutting and finishing stockings.	Higher prevalence of all chronic respiratory symptoms (dyspnea, sinusitis, and nasal catarrh); acute systems (cough, throat dryness) and decreased lung function in exposed vs control
(Valic & Zuskin, 1977)	Various textile workers	One cohort exposed to synthetic fibers only (poly- acrylonitrile fibers); the others exposed to hemp or cotton dust (before exposure to synthetic fibers) [TD =1.04 mg/m^3, RD =0.53 mg/m^3]	Lower prevalence of respiratory symptoms in synthetic fiber workers compared to hemp and cotton; however, the synthetic-only worker group was exposed to lower total and respirable dust levels.
(Goldberg & Theriault, 1994)	Synthetic textile workers	Retrospective cohort study	Mortality rates for all causes of death and colorectal cancers were low.
(De Roos et al., 2005)	Textile workers	Case cohort analysis [EU only]	>20 years of exposure associated with increased risk of colorectal cancers; dyes increased colon cancer.
(Pimentel et al., 1975)	Synthetic textile	Workers (7) and transfer of disease to guinea pigs. Textile fibers and dust examined.	Symptomatic (respiratory) workers, lung biopsies identified inflammation and damage. Only polyester antigens produced precipitins (not nylon, wool/ polyester).
(NIOSH, 2000)	Aramid	Case study of workplace exposures in two departments [TD <.099 mg/m^3, F<0.053 fibers/cm^3, acids]	Upper-respiratory symptoms reported (56% Spinning workers, 27% Finishing workers) (infected gland, sore throats, and infections).
(Mastrangelo et al., 2003)	Polyvinyl chloride	Nested case reference study of workers [TD>10 mg/m^3, RD = 4.5–50%]	Increased risk of lung cancer associated with exposure to PVC dust

Author(s), year	Industry	Study methodology [sampling type]	Findings
(Mastrangelo et al., 1979)	Polyvinyl chloride	Cohort study of 1216 workers [TD = 0.38–2.88 mg/m^3; RD =40.3%]	Pneumoconiosis in workers. Reported a low risk of lung cancer, but study separated by job and not job area.
(Chivers et al.,1980)	Polyvinyl chloride	Lung function tests of workers in from different exposure groups. [TD =0.2–11.5 mg/m^3]	No statistical difference between population exposed to PVC dust; solvents; or mixture of dust and solvents.
(Casula et al., 1977)	Polyvinyl chloride	PVC dust microscopy and [TD = 5–7 mg/m^3; RD>90%]	Study to characterize and estimate environmental dust at a PVC plant
(Jones et al., 1988)	Polyvinyl chloride.	Correlations between 5498 workers by occupation (during 1940–1974) and cancer type [TD= 0.23–2.88 mg/m^3]	Significant excess of non-secondary liver tumors with 11 deaths.
(Boffetta, et al., 2003)	Polyvinyl chloride	Meta-analysis of 6 worker studies.	Increased cancer risk in PVC workers from 6 studies.
(Gennaro et al., 2008)	Polyvinyl chloride and vinyl chloride	Comparing death-rates depending on job four categories [TD = 0.23–2.88 mg/m^3 for PVC Baggers in Jones et al., 1988]	Autoclave workers had highest liver tumor risks; PVC Baggers had significant risks for all deaths and cardiovascular disease deaths.

Note:

[1] Table shaded to separate the microplastic industries: flock, textile, polyvinylchloride (PVC).

[2] Abbreviations: EU = endotoxin units; CFU = colony forming units; RD = respirable dust; TD = total (inhalable) dust; F = Fibers. Only dust and fiber measurements were included in the table.

Table 3:

Markers of human or sentinel animal exposure and health effects

Study	Exposure	Markers	Health effect	Comment
(Schwabl et al., 2019)	Eight individuals in the general population	MP detection in all 8 humans' stools	NS	Marker of intake, but not uptake.
(Urban et al., 2000)	Breakdown of implants in 31 patients	PE particles <50 μm (most =1 μm) found in abdominal lymph nodes of 88% of patients (along with metal particles). Found in liver or spleen of 14% of patients	NS	Marker of breakdown and transport once internalized.
(Hicks et al., 1996)	Breakdown of implants in 5 patients	All lymph nodes of 5 patients had PE or metal debris.	Inflammatory response in lymph nodes shown to include immune response	Marker of breakdown, transport, and adverse health impact once internalized. Signs not observed in 7 patients without implants.
(Walker & Bullough, 1973)	Break down of PE hip replacement in dogs	Deposits of PE MP found in the alveolar walls of the lungs	NS	Indication of breakdown, transport, and health effect (secondary redistribution)
(Volkheimer, 1975)	Feeding and rectal administration of PVC to rats, guinea pigs, rabbits, chickens, dogs, and pigs	PVC particles (200 g) resulted in 10–15 particles/mL venous blood and detection in liver and other organs. GI uptake and para cellular transport of particles up to 130 μm.	NS	Markers to identify exposure and uptake. Differential uptake with age and sleep (active young absorbed more). Caffeine and cigarettes increased absorption.
(Volkheimer et al., 1969)	Microparticles in foods	Placenta into fetal circulation. Para cellular transport observed up to a diameter of 110 microns.	NS	Marker of transport of small particles.
(Volkheimer, et al., 2001)	Humans exposed to starch microparticles	After ingestion of 200 g starch, ~100 starch-granules were excreted in urine within 8 hours. Excreted into milk of lactating mothers and by transplacental transfer to fetal blood.	NS	Marker of exposure, uptake, and transport of microparticles (not MP- specific).
(Ward et al., 2002)	Study of effect of implant thickness and chemistry on rats	Studied thickness (300 vs 2000 microns) and use of solid PU vs PU-silicone, PE-oxide, PTFE, and PVA as well as media pore size	Porous and thicker implants (PVA and ePTFE) cause more angiogenesis than solid implants.	Indicates size, thickness, and porosity created different immune responses.
(Nichols, et al., 2013)	Summary of studies of differential properties of micro particles	Evaluated properties of micro sensor development. Studied size, shape and physiochemical properties of coatings (including plastics).	Particles >100 μm produce greater foreign body responses and fibrosis.	Indication of effect of large particles; shape and size are important, and capsules as large as 1.5 mm produce an effect.
(Veiseh et al., 2015)	Deliberate study to develop small biomonitoring devices	Rats and non-human primates inject/implanted with microspheres (hydrogels, ceramics, metals, and plastics)	Showed immune effect	Marker of transport and adverse health effect. Size was more important than material. Particles 0.5 mm vs 1.5 mm had differing effect at different times post-implantation. Larger particles caused a shift toward immune and wound healing and less inflammation.
(Andorko & Jewell, 2017)	Summary of various small biomonitoring sensors	Summary of various micro particles and effect studies for developing biosensors.	Immune response from physicochemical properties of the material	Includes MPs and NPs (and other materials). Marker of transport and health effect of micro and nanoparticles. Engineered immune therapy is studying size and shape to improve delivery.
(Hart et al., 2018)	10 bottlenose dolphins	Screening of 9 phthalate monoester metabolites. One or more phthalates detected in 71% of dolphin	NS	Phthalate is nonspecific urine marker of MPs, but dolphin exposure to plastics and plasticizers is different from human exposures.

Study	Exposure	Markers	Health effect	Comment
(Baini et al., 2017)	Whales and plankton	Phthalate esters (PAE) were 5–18 times higher in whale blubber than in plankton.	NS	Phthalate is nonspecific marker of MPs in blubber, despite the presence of MPs in plankton.
(CDC, 2019)	General population. NHANES 2003 – 2004 and 2013–2014	Phthalate metabolites detected in urine of most (2636) individuals indicates exposures to plastics or plastic solvents	NS	Sensitive marker (most at <ng/mL) of plasticizer exposure. No measurements of MPs. Suggestive of plastics exposure, uptake, and transport.
(CDC, 2019)	General Population. NHANES Addenda 2013–2014	Phthalates and phthalate alternative metabolites detected in urine	NS	Sensitive marker (ng/mL). Detection of metabolites of phthalate diesters and other alternative plasticizers (not MP).
ATSDR, 1995, 1997, 2001, 2012	Studies of people and animals	Phthalates metabolites detected in urine and feces	Metabolites cause reproductive and developmental toxicities in animals	Only phthalate links to exposure and effect, no association to MPs specifically.
(Kononenko & Haucke, 2015)	43 mammal studies of exposure to nanoparticles	Various methods of mammal exposure *in vitro* and *in vivo*.	Evidence of stimulation and suppression of immune system	Non-MP/NP specific. Indication that physical and chemical properties of nanoparticles affect immune system interactions and interfere with experimental assays.
(Garrett et al., 2012)	Mice orally administered chitosan nanoparticles	Particles recirculate from the GI tract (enterocytes), to liver and then to the gall bladder, before being re-released into the gut with bile.	Translocation	Non-MP/NP-specific suggestion of how MP would transport.

Source: Modified from Zarus et al., 2020 b; Note: Table is shaded to separate the study groups: MP markers of transport within the body of mammals; markers of uptake and transport; non-specific biomarkers in MP exposed mammals; availability of biomarkers in humans.

MP = Microplastics; NS = None shown; ng/mL = nanogram per milliliter; PE = Polyethylene; PVC = Polyvinylchloride; PU = Polyurethane; PTFE = polytetrafluoroethylene; PVA = porous polyvinyl alcohol sponge

Table 4:

Summary of evidence and data gaps for assessing human exposure and health effects to micro and nano plastics

Exposure Element	Evidence	MP data	NP data	Critical Data Needs
Air identified as containing MP	Measured directly	>10 μm particles characterized for indoor and outdoor (Dris et al., 2017)	None	Fine respirable particles (<10 μm) need characterization
Seafood identified as containing	Measured in GI of fish, crabs and bivalves	>10 μm particles characterized in GI mostly (Karami et al., 2017; Li et al., 2016; Yang et al., 2015; Su et al., 2017; Van Cauwenberghe & Janssen, 2014; Rochman et al., 2015; Waite et al., 2018)	None	Edible portions and NP <10 μm under are needed
Drinking water and beverages identified as containing	Measured directly	>10 μm particles characterized in many cities (Kosuth et al., 2018)	Very limited. A tea study provides some (Hernandez et al., 2019)	Fine respirable particles need characterization
Seasonings	Salt, Sugar, Honey	>10 μm particles characterized (Yang et al., 2015; Iñiguez et al., 2017; Kosuth et al., 2018; (G. Liebezeit & Liebezeit, 2013 & 2015)	None	Edible portions and NP <10 μm under are needed
Vegetables not characterized	In soils, in plankton	None	None	Full characterization is needed
Meats not characterized	In soils and in seafood scraps, PAEs in mammals, but not directly (Blasing & Amelung, 2018; Baini et al., 2017; Rochman et al., 2015, Li et al., 2016; Yang et al., 2015; Su et al, 2017; Van Cauwenbergh & Jansen 2014)	None	None	Full characterization is needed
Uptake and Absorption	**Evidence**	**MP data**	**NP data**	**Critical Data Needs**
Lungs	Measured directly in workers along with health effects and in animals	Measured in workers and in air (Burkhart et al., 1999; Pimentel et al., 1975; Chivers et al.,1980, Mastrangelo et al., 1979; Valic & Zuskin, 1977; Zuskin et al., 1998; Atis et al., 2005)	Measured in workers lungs (Eschenbacher et al., 1999; Kern et al., 1998) and to translocate to blood (Pauly et al., 1998)	Not studied in non-workers
Immune system	Polyethylene was found to translocate lymphatics in implant patients and related to immune response (and markers)	Measured to translocate in implant patients and found in lymph nodes of workers (Urban et al., 2000; Hicks et al., 1996; Walker & Bullough, 1973; Kern et al., 1998; Veiseh et al., 2015)	Measured to translocate in implant patients and animals (Kononenko & Haucke, 2015; Urban et al., 2000; Jung et al. 2020)	Not measured in general population. Polyethylene should represent other NP. Other nano particles have shown similar effects.
Neurologic	Polystyrene alters neurologic mouse cells only. Polyethylene association with dopamine in humans	Measured in biota, but effects might be associated with nano size (Kononenko & Haucke, 2015; Ward et al. 2002))	Measured to enter cells when applied and demonstrated effects (Andorko & Jewell, 2017; Kononenko & Haucke, 2015; Jung et al. 2020)	Not measured in general population. Full pathways of uptake are not demonstrated.
GI system	Measured in feces of general population, Implied by association with health effects in workers; GI cancers.	Measured to translocate in animals after inserted and cancers associated to work environment (Vobecky, Devroede, & Caro, 1984; (De Roos et al., 2005; Garrett et al., 2012)	Not directly measured, but suggested by movement of other nano particles (Volkheimer, 1975; Garrett et al., 2012	Human data on GI absorption us not known, but associated with effects; feces MP and urine PAEs are non-specific indicators

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Liver	Implied by association with health effects in workers only (Jones et al., 1988; Gennaro et al., 2008)	No exposures; injected microparticles circulated to liver (Volkheimer, 1975) Measured in liver and spleen of implant patients (Urban et al. 2000)	None	Not measured in workers, animals, or general population. But found in implant patients
Biomagnification of other toxicants	Measured directly as a factor >1x in marine animals, but no support for great magnification is demonstrated	Measured in marine environment and in fish GI tracks indicate a decrease in the trophic levels, not an increase. Thus, the increase to humans is expected to be slight (NAS 2020)	None	Data in human food supply is needed; however, total exposure to many persistent pollutants occurs routinely

1. The table is shaded to assist in identifying the largest data gaps for assessing microplastic exposure and effect. Red, identifies the largest data needs, yellow identifies a need for further characterization, and green identifies that there is sufficient characterization to demonstrate an element exists. These qualitative rankings are explained throughout the text.

2. Abbreviations: GI = Gastrointestinal system, MP = Microplastics, NP = Nanoplastics, PAE = phthalate esters, μm =micrometers