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Review

Potential Health Impact of Microplastics: A Review of Environmental Distribution, Human Exposure, and Toxic Effects

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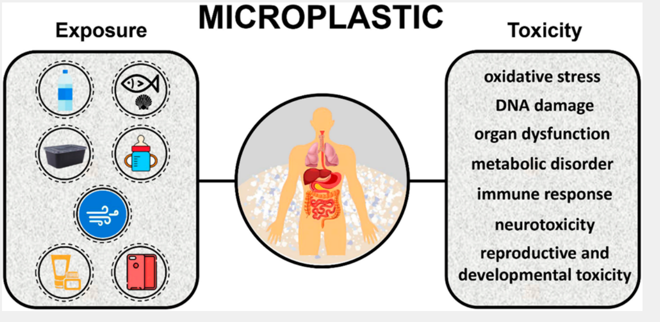
ABSTRACT: Microplastics are ubiquitous in the global environment. As a typical emerging pollutant, its potential health hazards have been widely concerning. In this brief paper, we introduce the source, identification, toxicity, and health hazard of microplastics in the human. The literature review shows that microplastics are frequently detected in environmental and human samples. Humans are potentially exposed to microplastics through oral intake, inhalation, and skin contact. We summarize the toxic effects of microplastics in experimental models like cells, organoids, and animals. These effects consist of oxidative stress, DNA damage, organ dysfunction, metabolic disorder, immune response, neurotoxicity, as well as reproductive and developmental toxicity. In addition, the epidemiological evidence suggests that a variety of chronic diseases may be related to microplastics exposure. Finally, we put forward the gaps in toxicity research of microplastics and their future development directions. This review will be helpful to the understanding of the exposure risk and potential health hazards of microplastics.



KEYWORDS: *microplastics, emerging pollutant, exposure pathway, toxicity, health hazards*

1. INTRODUCTION

Plastics are used worldwide. In 2019, the global annual output of plastic products reached 460 million tons, only 9% of which are recycled, and it is estimated that it will reach 1.2 billion tons by 2060.[1] High yield and low recovery determine that a large number of plastics enter the environment. Major commercial plastics in the market include polypropylene (PP), polyethylene (PE), polyethylene terephthalate (PET), polystyrene (PS), and polyvinyl chloride (PVC), etc.[2] Plastics produce small fragments or particles through crushing, splitting and degrading during use. In the 1970s, plastic particles were first discovered in surface waters of the Atlantic.[3] Thompson et al. published a paper in *Science* and put forward the concept of "microplastics" for the first time.[4] Microplastics refer to plastic fragments and particles with a diameter of less than 5 mm. They are called nanoplastics when the diameter is less than 1 μm. In fact, the particle size of microplastics ranges from a few microns to a few millimeters. Different with engineered nanomaterials, it is a mixture of heterogeneous plastic particles with various shapes, which is becoming an emerging issue for human health.[5] In addition to the larger plastics, microplastics are also specially produced and added to personal care products such as facial cleansers and cosmetics.[6] Industrial production, such as synthetic textile industry, flocking industry, and plastics industry, also produces a large number of microplastics. It is found that about 65 million microplastic particles are released into the water every day after being treated by the sewage treatment plant.[7]

Microplastics are detected from the south to Antarctica,[8] north to the Arctic,[9] up to the peak of Mount Everest,[10] and down to the Mariana Trench.[11] Plastic is the largest part of marine garbage.[12] In 2017, more than eight million tons of plastics entered the oceans, and the amount is >33 times as much as that of the total plastics accumulated in the oceans by 2015.[13] However, due to the limitation of capture methods, the content of microplastics in the environment may be underestimated. Lindeque et al. shows that the microplastic concentration when nets with a 100 μm mesh are used is 2.5-fold and 10-fold greater than that when 333 and 500 μm meshes are used, respectively.[14] They also estimate that microplastic concentrations might exceed 3700 microplastics m^{-3} when nets with a 1 μm mesh size are used. Microplastics may reduce the availability of nutrients in microalgae[16] or be directly ingested by organisms, causing greater impact on the food web through the bioaccumulation of the food chain.

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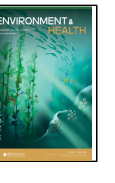

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Plastic pollution is one of the most serious environmental challenges in the 21st century. It is discussed by the United Nations Environment Assembly (UNEA) and a historic resolution, entitled "End plastic pollution: Towards an international legally binding instrument", was adopted.[15] Microplastics in the real environment have extremely complex sources with more diversified occurrences and more hidden hazards, which brings about great challenges in revealing their toxic effects and potential health hazards. In order to determine the risk of microplastics to human health, one of the main problems is the lack of information about microplastics to which humans are exposed.[6] The qualitative and quantitative analysis methods of microplastics in the real environment limit the research on their source, occurrence, and toxicity.[17]

Toxicological studies on microplastics are increasing rapidly. Experiments show that the exposure to microplastics induces a variety of toxic effects, including oxidative stress, metabolic disorder, immune response, neurotoxicity, as well as reproductive and developmental toxicity.[18] However, limited by the existing technical methods, there is no systematic research on the absorption, metabolism, migration, transformation, and accumulation of microplastics. The knowledge gap also exists in potential toxic effects and health hazards, e.g., the key factors determining the toxic effects of microplastics. This review briefly summarizes the pathways of human exposure to microplastics and the detection of microplastics in organisms and human bodies and focuses on the current research progress of the toxicity of microplastics. Then we suggest future development directions.

2. PATHWAYS OF HUMAN EXPOSURE TO MICROPLASTICS

Microplastics pose a potential threat to human health due to their common existence in the environment and the reported toxic effects. It is important to understand the pathways of human exposure to microplastics. Oral intake, inhalation, and skin contact are the common ways (Figure 1). Among them, oral intake is the main exposure route.[19] In fact, people are often exposed to microplastics in multiple ways simultaneously. Rillig et al. proposes the concept of "plastic cycle" in *Science*, which means microplastics can migrate between different environmental media.[20] The movement of microplastics increases the risk of human exposure.

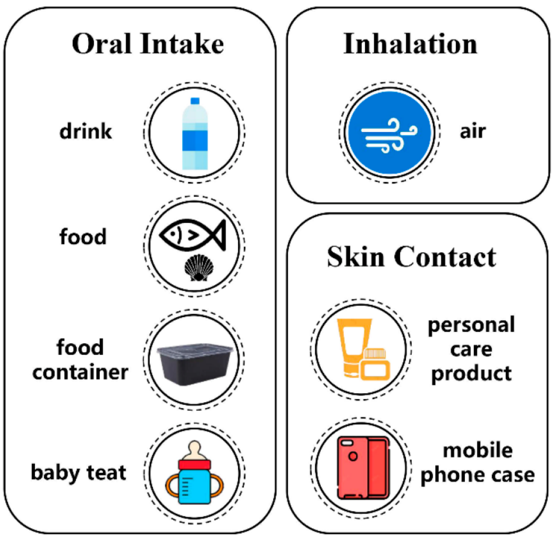

Figure 1. Pathways of human exposure to microplastics.

2.1. Oral Intake

Microplastics exist in our daily necessities like drinking water, bottled water, seafood, salt, sugar, tea bags, milk, and so on.[21−29] Europeans are exposed to about 11,000 particles/person/year of microplastics due to shellfish consumption,[30] and according to food consumption, the intake of plastic particles in human body is 39,000−52,000 particles/person/year.[31] Microplastics may also have been widely distributed in soil, especially in agricultural systems.[20] They (especially with negative charge) can get into the water transport system of plants, and then move to the roots, stems, leaves, and fruits.[32,33] Once microplastics enter agricultural systems through sewage sludge,[34] compost,[35] and plastic mulching,[36] they will cause food pollution, which may increase the risk of human exposure.

Take-out food containers made of common polymer materials (PP, PS, PE, PET) are used widely, from which microplastics are found.[37,38] It is estimated that people who order take-out food 4−7 times weekly may intake 12−203 pieces of microplastics through containers.[38] In addition, research demonstrates that the surface of silicone rubber baby teats degrades when they are sterilized by steam, during which microplastic particles are released into the environment.[39] It is estimated that the total number of microplastic particles entering the baby's body during one year of normal bottle feeding reaches about 0.66 million.

2.2. Inhalation

Microplastics in the air are mainly PE, PS, and PET particles and fibers with size ranges of 10−8000 μm.[40] The largest source of microplastics (84%) in the atmosphere comes from the road.[41] It is reported that the median concentration of microplastic fibers is 5.4 fibers/m^3 in the outdoor air and 0.9 fibers/m^3 in the indoor air in Paris.[42] The average concentration of microplastics is 1.42 particles/m^3 in the outdoor air in Shanghai, and the size range is 23−5000 μm.[43] It is estimated that annual microplastics consumption ranges from 74,000 and 121,000 particles when both oral intake and inhalation are considered.[31] Amato-Lourenço et al. detected microplastic particles smaller than 5.5 μm and microplastic fibers with the size of 8.12−16.8 μm in human lungs, whose main components are PE and PP.[44] The size of microplastics detected in lung tissue is smaller than that in the atmosphere. This further confirms that humans can be exposed to microplastics by inhalation and prompts attention to the potential harm to the human body.

2.3. Skin Contact

Microplastics are usually considered not to pass through the skin barrier,[45] but they can still increase exposure risk by depositing on the skin.[46] For example, the use of consumer products containing microplastics (such as face cream and facial cleanser) will increase the exposure risk of PE.[47] The protective mobile phone cases (PMPCs) can generate microplastics during use, which are transferred to human hands.[48] When children crawl or play, they may come into contact with microplastics on the ground. During the dermal exposure of microplastics, some typical plastic additives, including brominated flame retardants (BFRs), bisphenols (BPs), triclosan (TCS), and phthalates, may be absorbed.[49]

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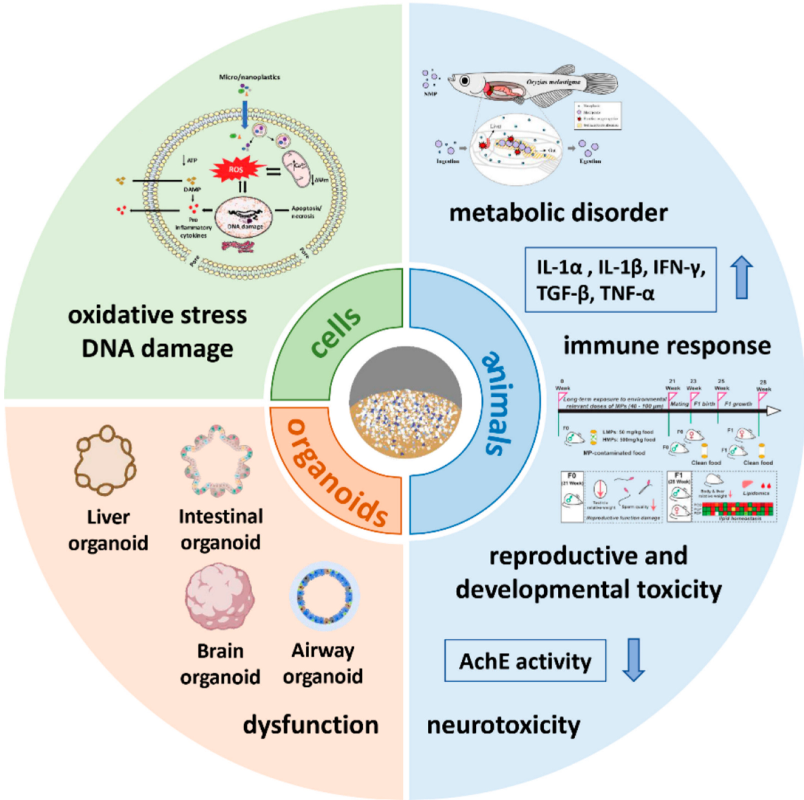

Figure 2. Toxicity mechanism of microplastics. Cells: oxidative stress and DNA damage. Reproduced with permission from ref 74. Copyright 2021 Elsevier. Organoids: dysfunction. Animals: metabolic disorder, immune response, neurotoxicity, as well as reproductive and developmental toxicity. Reproduced with permission from ref 83. Copyright 2021 Elsevier. Reproduced from ref 99. Copyright 2022 American Chemical Society.

3. DETECTION OF MICROPLASTICS IN ORGANISMS AND HUMAN

Microplastics are found in animals. They pose a great threat to aquatic organisms, like fish and marine mussels. Microplastic fibers are the most frequent microplastic type ingested.[50] All fishes in the Haizhou Bay have microplastics with the highest abundance of 22.21 ± 1.70 items/individual.[26] Mussels in the French Atlantic coast and the coastal waters of the U.K. both have microplastics.[27,51] For wild coastal animals, microplastics are found in their intestine, stomach, liver, and muscle.[52] PET is also detected in the feces of pets, such as cats (<2300−340,000 ng/g) and dogs (7700−190,000 ng/g).[53] Microplastics also exist in plants and algae. Liu et al. carried out a hydroponic experiment, which they confirmed using confocal laser scanning microscopy that microplastics can transfer from roots to the aboveground parts of rice seedlings.[54] Yan et al. reports that microplastics are internalized in the vacuoles of algal cells.[55] It is noteworthy that the phenomenon of biological endocytosis of microplastics can be utilized to remove microplastics from the environment. Manzi et al. summarizes the algal species that have been used to remove microplastics from the aquatic environment and highlights the mechanism of microplastics biodegradation.[56]

It is generally believed that after entering the human body, microplastics will be excreted out through the gastrointestinal tract and biliary tract. However, researchers detect the existence of microplastics in human blood.[57] People begin to reconsider the harm of microplastics to human health. The intake, distribution, accumulation, and metabolism of microplastics in the human body are attracting more and more attention. Understanding the concentration of microplastics in the human body is an important prerequisite for exploring their potential harmful effects. A recent review indicates that microplastics are transported to the whole body through blood circulation, and the existence of microplastics are found in 15 human biological components, such as the spleen, liver, colon, lung, feces, placenta, breastmilk, etc.[58] The organs with high content are the colon (28.1 particles/g) and liver (4.6 particles/g). The main types of microplastics detected include PE, PET, PP, PS, PVC, and PC.

Pregnant women and infants are sensitive people exposed to microplastics.[59] The concentration of PET in infant feces (5700−82,000 ng/g, median: 36,000 ng/g) is ten times higher than that in adults (2200−16,000 ng/g, median: 2600 ng/g),[60] indicating that the exposure level of microplastics in infants may be much higher than adults. Twelve microplastic fragments, ranging from 5 to 10 μm, are detected in human placenta by the team of Ragusa for the first time,[61] and then they first detect PVC and PP microplastics with a size of 2−12 μm in human breastmilk.[62] Since then, more studies also detect microplastics in placenta, meconium, and breastmilk. Zhu et al. detects microplastics in 17 placental samples and identifies 11 types of polymers with sizes from 20.34 to 307.29 μm.[63] Liu et al. recruits 18 pairs of mothers and infants and determines 16 types of microplastics in placenta, meconium, infant feces, breastmilk, and infant formula samples.[64] More than 74% of microplastics are 20−50 μm in size. In accordance with the DOHaD theory, adults experiencing adverse factors in the early stages of development will increase the probability of obesity, diabetes, cardiovascular disease, and other chronic diseases in adulthood.[65] The appearance of microplastics in

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Environ. Health 2023, 1, 249−257

Table 1. Representative Studies on the Exposure Experiment of Microplastics Using Human Organoids

organoids	microplastics	exposure conditions	toxic effects	ref
airway organoids	polyester fibers from the drying of synthetic clothes and fabrics, 700 ± 400 μm	1, 10, and 50 μg/mL for 1 week	fibers can get into the cellular layer and cause a significant reduction of SCGB1A1 gene expression, which is considered to be a biomarker of lung injury	79
forebrain organoids	PS, 1, 10 μm	5, 50, and 100 μg/mL for 7 and 27 days	PS can lead to adverse effects on the development of embryonic brain-like tissue; contrary to short-term exposure, long-term PS exposure reduces cell viability	80
intestinal organoids	PS, 50 nm	10 and 100 μg/mL for 1 and 2 days	PS distinctly accumulates in various type cells in intestinal organoids, causing the cell apoptosis and inflammatory response; active endocytosis plays an essential role in the microplastics uptaking into enterocyte cells	81
liver organoids	PS, 1 μm	0.25, 2.5, and 25 μg/mL for 48 h	PS can induce hepatotoxicity, disrupt lipid metabolism, and increase the levels of HNF4A and CYP2E1 in the liver organoids specifically	82

human placenta further emphasizes that these nondegradable chemicals have potential intergenerational influence on the human body and may affect the developing fetus. Therefore, more attention should be paid to the potential impact of early exposure of infants and early development of embryos.

4. TOXIC EFFECTS OF MICROPLASTICS

Microplastics producing toxic effects is a complex process and is affected by many factors including the physical and chemical properties, exposure time, additives, etc. Microplastics are not only toxic itself but also carriers for many pollutants to enter biological tissues and organs. We aim to systematically sketch their potential toxicity at the "individual-tissue-cell-subcellular" level, which will help to explore the toxicity mechanism. Due to the lack of direct research from humans, this section briefly summarizes the major effects of microplastics in present experimental models, like cells, organoids, and animals (Figure 2).

4.1. Factors Affecting the Toxicity of Microplastics

There are many factors that may influence the toxicity of microplastics, including size, shape, surface charge, weathering/aging process, adsorption, etc.[66] Larger particles are less likely to enter cells and result in lighter oxidative stress.[67] Compared with spherical microplastics, randomly shaped fragments cause more harmful physical effects.[68] Surface charge of microplastics is the major parameter determining cellular uptake efficiency. Zeta potential is positively correlated with the number of internalized particles.[69] After undergoing a weathering/aging process, the physical and chemical properties of plastic will change, such as color, surface morphological, crystallinity, particles size, and density.[70] Besides, microplastics typically include material composed of polymers as well as additives. With changes in the environment, additives in microplastics may be released and produce toxicity.

Due to the surface energy caused by their small size, microplastics may act as the vector adsorbing other pollutants, especially heavy metals and hydrophobic organic chemicals (HOCs), which may enhance toxicity.[71] In marine and coastal environments, microplastics can adsorb heavy metals varying from 10^{-1} to 10^{4} μg/g and organic pollutants depending on hydrophobicity.[70] Once further degrading into nanoplastics, when they contact various biomolecules (e.g., proteins), a biomolecule corona can quickly form and further alter their persistence, bioavailability, and ecotoxicity.[72] In addition, aging processes can alter the protein corona constitution.[73]

4.2. Toxic Effects in Cell Experiments

Banerjee et al. reviews the biological effects of microplastics in mammalian cells, including gastrointestinal cells, airway cells, immune cells, and others.[74] Cytotoxicity of microplastics varies with cell type, particle size, dose, charge, exposure time, type, and additives, causing cell deaths mainly by oxidative stress and membrane damage. Rubio et al. summarizes the biological effects of microplastics in different human hematopoietic cell lines, and the results show that microplastics cause oxidative stress and DNA damage with high variability between cell lines.[75] In addition, microplastics can inhibit the growth of microalgae cells and damage the antioxidant system depending upon their relative particle size.[55,76] Microplastics with different physical and chemical properties induce different immune responses. Fuchs et al. reports that amino-modified PS ($PS\text{-}NH_2$) inhibits the phagocytosis of M1 and M2 macrophages, while carboxyl-modified PS (PS-COOH) does not affect the phagocytosis of M2.[77]

4.3. Toxic Effects in Human Organoid Experiments

Human organoids are the latest development of in vitro models and have been used as new exposure models for emerging contaminants like microplastics. Compared with cells and animals, human organoids can better reflect the harm of microplastics to the human body. At present, the organoids that have been used for microplastics include airway organoids, forebrain organoids, intestinal organoids, and liver organoids (Table 1). After microplastics exposure, all of the organoid models exhibit functional disorder. Cheng et al. further studies the combined effect of PS and bisphenol A (BPA) using liver organoids on the basis of their previous research.[78] The results show that PS and BPA have synergistic hepatic effect, indicating the carrier function of microplastics. The ERα and HNF4A are proposed as potential biomarkers.

4.4. Toxic Effects in Animal Experiments

4.4.1. Metabolic Disorder. Previous animal experiments confirm that microplastics lead to the dysfunction of the liver and intestine. For instance, Kang et al. finds that microplastics induce intestinal damage of fish by two different mechanisms.[83] PS with size of 50 nm exhibits stronger oxidative stress, while PS with size of 45 μm causes significant imbalance of intestinal flora. Kim et al. reports that microplastics lead to the inhibition of digestive enzyme activity in fish through a microalgae-crustacean-small yellow croaker food chain.[84] Jin et al. also reports that intestinal barrier and metabolic function are impaired in PS exposed mice.[85] Tan et al. demonstrates that microplastics significantly reduce lipid digestion in the simulated human gastrointestinal system, and PS shows the highest inhibition.[86] The decrease of lipid digestion is independent of PS size. Lu et al. reveals that PS exposure causes the local infection and lipid accumulation in the liver of fish and disrupts the energy metabolism.[87] In addition, Deng et

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Environ. Health 2023, 1, 249−257

al. discovers that after exposure to microplastics and organophosphorus flame retardants (OPFRs), the metabolites of mice change significantly.[88] And it is noticeable that microplastics aggravate the toxicity of OPFRs, highlighting the health risks of microplastic coexposure with other pollutants.

4.4.2. Immune Response. Microplastics can induce immune response in the body. Yuan et al. reports that PE exposure activates the intestinal immune network pathway of zebrafish and produces mucosal immunoglobulin.[89] Li et al. demonstrates that the secretion of IL-1α is increased in the serum of rats exposed to PE but decreased in the Th17 and Treg cells among CD4$^+$ cells.[90] Lim et al. observes that inhalation of PS causes the upregulated expression of the inflammatory protein (TGF-β and TNF-α) in lung tissue of rats.[91] Liu et al. finds that PS exposure significantly increases the expression of inflammation factors (TNF-α, IL-1β, and IFN-γ) in mice, and intestinal immune imbalance will significantly increase the accumulation of microplastics, producing further toxic effects.[92]

4.4.3. Neurotoxicity. Microplastics are also toxic to the neural development. Inhibition of acetylcholinesterase (AchE) activity is the most reported neurotoxic effects after the exposure of microplastics.[93] In a study of juvenile fish, the microplastics inhibit the activity of AchE, increase lipid oxidation in the brain, and change the activities of energy-related enzymes, eventually causing neurotoxicity.[94] Prüst et al. also reports that microplastics cause the abnormal behavior of nematodes, crustaceans, and fish.[93] Yang et al. discovers that PS (70 nm) can pass through the epidermis of larvae and enter into the muscle tissue.[95] It can destroy nerve fibers, decrease the activity of AchE, and exert great adverse effects on larval movement. Besides, Jin et al. reveals that after the chronic exposure to PS at environmental pollution concentrations (100 and 1,000 μg/L), the blood-brain barrier of mice is damaged, and the learning and memory dysfunctions occur.[96]

4.4.4. Reproductive and Developmental Toxicity. The effect of microplastics on reproduction is reflected in the development of germ cells and embryo quality. For example, Liu et al. finds that the PS exposure affects the development of female mouse follicles and the maturation of oocytes, reducing the quality of oocytes.[97] And Hu et al. reports that microplastics might cause adverse effects on pregnancy outcomes through immune disorders.[98] Deng et al. finds that after long-term exposure to environmentally relevant doses of PS, the sperm quality significantly decreases, which affects the fertility of male mice.[99] In addition, Park et al. shows that the number of live births per dam and the sex ratio and body weight of pups in groups treated with PE are notably altered.[100] What's more, they suggest the IgA level as a biomarker for harmful effects following exposure on microplastics.

4.5. Epidemiological Investigation

Epidemiological investigation is a good method to demonstrate the correlation between microplastics exposure and adverse health outcomes. However, there are relatively few epidemiological studies related to microplastics. Kremer et al. reports that due to occupational exposure, workers in polymer factories in The Netherlands are more likely to suffer from chronic respiratory diseases.[101] In Canada and the United States, nylon flocking factory employees are diagnosed with work-related interstitial lung disease.[102] Yan et al. discovers that the fecal microplastic concentration in inflammatory bowel disease (IBD) patients is significantly higher than that in healthy people, and the concentration is positively correlated with the degree of IBD.[103] Horvatits et al. finds the existence of microplastics in cirrhotic liver tissues, whose concentration is higher compared to that of liver samples from healthy individuals.[104] Wu et al. detects the existence of microplastic in human aortic dissection thrombus samples and human acute arterial embolism samples.[105] These results suggest that microplastics may be associated with the formation of many chronic diseases, which may be harmful to human health.

5. CONCLUSIONS AND PERSPECTIVE

Humans are exposed to microplastics by oral intake, inhalation, and skin contact. Microplastics have been found in a variety of organisms and multiple parts of the human body. We emphasize the potential impact of microplastics on the early exposure of infants and the early development of embryos. At present, the toxicity research on microplastics show that the exposure will cause intestinal injury, liver infection, flora imbalance, lipid accumulation, and then lead to metabolic disorder. In addition, the microplastic exposure increases the expression of inflammatory factors, inhibits the activity of acetylcholinesterase, reduces the quality of germ cells, and affects embryo development. At last, we speculate that the exposure of microplastics may be related to the formation of various chronic diseases. Although the toxicity of microplastics has been widely studied, there are still several key scientific issues that need to be further explored: (1) The key technologies for precise identification, multiscale characterization, and accurate quantitative and dynamic tracing of microplastics in organisms. At present, the commonly used analytical means can detect microplastics only at the micron level, and it is difficult to effectively analyze microplastics with smaller size (nanoplastics) and greater potential harm, which brings great challenges to accurately reveal the possible health risks of microplastics. In addition, there is still a lack of effective dynamic tracing means. Therefore, how to precisely identify, accurately quantify, and dynamically trace the microplastics in organisms is the primary problem. It may be improved by comprehensively utilizing existing imaging and analysis technologies, such as SEM, CLSM, Raman spectroscopy, and so on. (2) The biological processes such as absorption, metabolism, transportation, and accumulation of microplastics, as well as crossing biological barriers. Although studies have shown that microplastics can enter the circulatory system and reach other tissues, from the current research results, one cannot clearly determine the key factors of the bioprocess of microplastics. Systematic research on the key biological processes of microplastics needs to be carried out at the "individual-tissue-cell-subcellular" level. The content includes but is not limited to the transport process, the distribution in tissues and organs, the single cell atlas, and the intracellular localization. (3) The "common" and "specific" characteristics of biological processes of different microplastics. There are various kinds of microplastics with different sizes and physical and chemical properties. However, the current experiments usually use PS and PE as models, and most of them are commercially synthesized, which means the type of microplastic is unitary. Therefore, more kinds of microplastics (e.g., actual environmental samples) need to be used in the exposure experiments, and their commonness and specificity should be revealed. (4) The "real" quantitative relationship between the exposure dose and toxic effects of microplastics, as

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Environ. Health 2023, 1, 249−257

well as the combined toxic effect of microplastics and other pollutants. Although scientists have found some toxic effects about the exposure of microplastics using multiple experimental models, they usually use high exposure doses. It is necessary to evaluate the toxic effects of microplastics more realistically from the perspective of actual environmental concentration and the whole life cycle of organisms. Because of the large surface energy, microplastics usually adsorb other pollutants, especially heavy metals and hydrophobic organic chemicals. The combined toxicity needs further investigation to explore whether there is synergy between microplastics and adsorbed pollutants and the toxic mechanism. (5) The key determinants and molecular mechanisms of toxic effects of microplastics. At present, the research on the toxicity of microplastics is mostly effect analysis, and the molecular mechanism is relatively lacking. It is necessary to combine the multiomics analysis with toxicity effect study, in which the exposure and effect biomarkers with high sensitivity and specificity may be screened. (6) The correlation between microplastics and adverse health outcomes. Almost all the studies on the toxicity of microplastics use experimental models, and the harm to the human body is still unclear. Epidemiological and clinical data needs to be collected. Biomarkers can be used to explore the internal relationship between microplastic exposure and possible adverse health outcomes. A health risk assessment model should be established with the help of machine learning to early warn the exposure risk of microplastics.

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Notes

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