Harmful effects of microplastic pollution on health of animals. A Literature Review

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Background. Environmental pollution by microplastics is a global problem that has arisen from the extensive production and use of plastics. Small particles of different types plastic with a diameter of less than 5 mm are found around the globe in water, air, soil, and various living organisms. An individual constantly absorbs microplastics with water and food, inhales with air. Therefore, an important issue of microplastic environmental pollution is whether it poses a risk to human health. **Objectives:** Experimental studies of the potential health risks of microplastic are now under the undoubted scientific interest. The number of publications on this topic is growing every year. However, it could be difficult to analyze the potential data because of narrow investigations and contradictory results obtained, which should be combined and generalized. In this review we tried to systematize and summarize the microplastics effect on the health of different classes animals. This manuscript could be relevant for ecologists, experimental biologists, and physicians dealing with problems related to anthropogenic environmental changes. **Methodology**. We checked PubMed and Scopus from 01/2010 to 09/2021 for peer-reviewed scientific studies concerning the 1) environmental microplastic pollution, 2) human microplastics consumption, and 3) the microplastics impact on animal health. **Results.** At present, a fairly large number of studies concerning the effect of microplastic particles on aquatic organisms were carried out. It was demonstrated that in aquatic invertebrates, microplastics cause a decrease in feeding behavior and fertility, a slowdown in the growth and development of larvae, an increase in oxygen consumption and production of its active forms, etc. In fish, microplastics, depending on the particle size, dosing and duration of exposure, can lead to structural damage to the gastrointestinal tract, liver, gills and even the brain, as well as cause metabolic disturbances, affect behavior and fertility. There are very few data on the effect of microplastics on terrestrial mammals. Currently, there are only 30 papers in the PubMed and Scopus databases that have studied the effects of microplastic on laboratory mice and rats, with half of these papers published in 2021, indicating the growing interest of the scientific community in this issue. It was demonstrated that in mice and rats, microplastics can cause biochemical changes, structural damage and dysfunctions of the intestines, liver, kidneys, reproductive system, etc. **Conclusions.**Microplastics is known to pollute seas and negatively affect the health of aquatic organisms. Studies on laboratory mice and rats demonstrate that microplastics can provide negative influence on human health. However, due to the small number of studies and significant variation in experiments in plastic types, particle sizes, dosing, model and mode of administration, the data obtained are quite fragmentary and contradictory.

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Abstract

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Methodology. We checked PubMed and Scopus from 01/2010 to 09/2021 for peer-reviewed scientific studies concerning the 1) environmental microplastic pollution, 2) human microplastics consumption, and 3) the microplastics impact on animal health.

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Conclusions. Microplastics is known to pollute seas and negatively affect the health of aquatic organisms. Studies on laboratory mice and rats demonstrate that microplastics can provide negative influence on human health. However, due to the small number of studies and significant variation in experiments in plastic types, particle sizes, dosing, model and mode of administration, the data obtained are quite fragmentary and contradictory.

Introduction

The term "plastics" refers to any materials based on synthetic or natural high molecular weight compounds - polymers. Plastics were widely used since the 1950s in many industries due to their low cost, versatility, low weight and durability. Over the past 60 years, more than 6.3 billion tons of various plastics have been produced worldwide, about 9% of which were recycled into secondary raw materials, and about 12% were utilized by incineration (Alabi et al., 2019). Plastic waste degrades very slowly in the environment. According to estimates of the specific plastics degradation rate, decomposition of 1 mm thick plastic fragment will take from several decades to hundred years, depending on its chemical content and environmental conditions (Chamas et al., 2020). However, plastic products disintegrate into small pieces. Plastic fragments less than 5 mm in size are called "microplastics" (MP). In a number of works, the term "nanoplastics" (NP) is described separately referring to plastic particles less than 100 nm in size. According to the source of origin, two types of MP are distinguished: 1) primary MP - deliberately created small particles of plastic for consumer and industrial use, such as abrasives in cleaning and detergents, cosmetics, polymer carriers for drug delivery, sandblasting, plastic coated fertilizers; 2) secondary MP - originates from fragmentation of large plastic debris (Hirt & Body-Malapel, 2020; Yee et al., 2021).

Due to the small size of the particles, MP is distributed in the environment with water and wind. MP could be detected all over the globe: in air, soil and water, polar ice, at the depths of the seas, in living organisms (Fackelmann & Sommer, 2019).

The mechanisms of the MP effect on living organisms are due to its physical and chemical properties. The chemical properties of the MP are determined by the chemical nature of the polymer and the properties of the additives. Particles of polyethylene (PE), polypropylene (PP) and polystyrene (PS) predominate among the polluting MPs. To provide the plastic with specific properties, inert or reinforcing fillers could be added: plasticizers, antioxidants, UV stabilizers, lubricants, dyes and flame retardants. Physical properties are size, shape, elasticity, and shear strength of MP particles, their surface charge. According to their shape, the particles are divided into fibers, grains, granules, fragments, films and foams. In addition, due to the high ratio of surface area to volume of particles, MP is capable to adsorb many pollutants and microorganisms on its surface (Campanale et al. 2020; Wright et al., 2020).

The aim of this review is to systematize and summarize the results of experimental studies of the microplastics effect on the health of different animals and to estimate the potential risk of microplastics to human health. The review discusses the levels of environmental microplastics pollution, estimates the consumption of microplastics by humans, and describes the effects of microplastics on animal health.

Special attention will be paid to experimental studies of the microplastics effects on laboratory rodents. The mouse and rats are the most commonly used model organisms in human disease research. Rodent models have been used widely to understand the mechanisms of many diseases, to examine the efficacy of candidate drugs and to predict patient responses. Therefore, data on the MP effects in mice and rats can help assess the possible risks to humans.

Survey methodology

We checked PubMed and Scopus databases for peer-reviewed scientific studies from 01/2010 to 09/2021 regarding the 1) environmental microplastic pollution, 2) human microplastics consumption, and 3) the microplastics impact on animal health.

1) We used the terms "microplastic pollution" in search query. For the detailed search, terms "soil", "air", "water", or "ocean" were used in the query.

2) We used terms "microplastic food", "microplastic human" and "microplastic human consumption" in the query to search for information about the human consumption of MP.

Many original papers and reviews were published on these topics. So, over the past 5 years from 2017 to 2021, 3569 publications were revealed in PubMed for the query "microplastic pollution", 584 belong to reviews, systematic reviews and meta-analysis. Accordingly, for the query "microplastic food" were found 986 publications and 194 of them were reviews, for the query "microplastic human" - 1040 and 292 respectively. In the review, we tried to give readers a general idea of the level of environmental pollution by microplastics and its significance for humans in order to demonstrate the relevance of the problem. So, we tried to include the most recently reviewed articles. Twenty reviewed articles describing the MP spreading in the environment, living organisms and in human food were analyzed.

3) We used terms "microplastic animal", "microplastic hazard", or "microplastic toxicity" in search query for search information about the impact of microplastics on animal health at the first step. We analyzed the results of the search from the most recent reviews.

According to these works, the MP danger to the aquatic organisms was investigated for a long time according to many various publications about this topic. Over the past 5 years in PubMed there were more than 700 publications concerning the effects of microplastic only on fishes, 73 were reviews. Therefore, in this review, we provided the brief information, obtained from recent reviews on aquatic invertebrates (Haegerbaeumer et al., 2019) and fish (Yong, Valiyaveetill & Tang, 2020).

For the harm assess of various substances to human health, mice and rats most often are used as model organisms. Thereafter, we focused our attention on articles on microplastic effects on laboratory rodents. Pubmed and Scopus databases were examined with the keywords "microplastic mouse" and "microplastic rat" from 01/2010 to 9/2021.

Inclusion criteria were studies performed on mice and rats, published in English and listed in MEDLINE (PubMed) or Scopus from January 1st, 2010 onwards; we included original experimental *in vivo* studies, tested microparticles of any polymer types.

Exclusion criteria were publications prior to January 1st, 2010; lack of an English translation; *ex vivo / in vitro* studies; and we excluded commentaries, summaries, reviews, editorials, and duplicate studies.

The earliest article that corresponds with our criteria was published in 2017. Thirty works published for the period from 2017 to 2021 matched to the specified requirements. We analyzed and summarized the parameters of microplastics exposure (type of plastic, particle size, dose, exposure time) and effects on animals' health.

Results

Methods for determining the content of microplastics

Determining the MP content in various natural and biological samples is not an easy task. The low concentration of MP particles, the variety of their chemical nature, shape and size, as well as a large number of natural polymers and oligomers, which are difficult to separate from synthetic plastic particles, significantly complicate the evaluation of the MP content in various media. In addition, the number of MP particles in similar samples obtained from different sources can vary significantly. Determining of the MP content in kitchen salt, depending on the place of its production and the research method, range from the absence of detectable plastic particles to 5400 particles per kilogram (Kwon et al., 2020).

To evaluate the MP content, the sample firstly was purified from natural organic polymers. For this purpose, in liquid samples such as water, dissolved sea salt and honey, the use of hydrogen peroxide is sufficient. Alkalis (KOH, NaOH), Fenton's reagent (Fe^{2+} ion with H_2O_2), acids (HNO_3, $HClO_4$), and digestive enzymes (proteinase, trypsin, and collagenase) are also used to isolate MP from tissues of living organisms, in addition to H_2O_2. The sample was passed through the filter. The number of MP particles on the filter was counted using microscope. To identify type of plastic FT-IR (Fourier Transform Infrared Spectroscopy) or Raman spectroscopy were used. (Kwon et al., 2020).

Microplastics environmental pollution

About 60-80% of the garbage on Earth consists of plastic, and almost 10% of its annual production ends up in the oceans, where the destruction of various plastic objects can take several hundred years (Avio, Gorbi & Regoli, 2017). It is estimated that more than 8 million tons of plastic enter the oceans annually (Erni-Cassola et al., 2019). Quantifying the global abundance and mass of oceanic plastic is difficult and therefore the available data are inconsistent. According to primarily estimates, the world's oceans contain at least 5.25 trillion plastic particles weighing 269 thousand tons (Eriksen et al., 2014). High concentrations of plastic waste are observed in the central circulation in the North Pacific Ocean. This accumulation of anthropogenic debris is called the Great Pacific Garbage Patch, or the Eastern Garbage Continent. According to modern estimates, the patch is about 1.6 million km^2 size, contains at least 79 thousand tons of plastic, of which about 8% is MP (Lebreton et al., 2018). Currently, a total of 5 oceanic circulations with plastic have been identified (in the North and South Atlantic Ocean, South Indian Ocean, North and South Pacific Ocean) (Avio, Gorbi & Regoli, 2017). The most common types of plastics in the marine environment are polyethylene (PE, about 23% plastic particles), polyesters-polyamides-acrylics (PP&A, 20%); polypropylene (PP, 13%) and polystyrene (PS, 4%). The concentration of plastic particles in tidal sediments is about 10^3-10^4 particles/m^3, in surface waters 0.1-1 particles/m^3, and there prevail plastics with a low density - PE and PP, in deep-sea sediments there are more than 10^4 particles/m^3, PE and PP are not detected in them and PP&A and chlorinated polyethylene (CPE) predominate (Erni-Cassola et al., 2019).

Rivers are the main channels for transporting plastic waste from land to seas. Rivers bring 1.15 to 2.41 million tons of plastic waste into the world's ocean each year. The MP content in fresh water reservoirs in North and South America varies from 0.16 to 3438 particles/m^3, in European rivers - from 0.28 to 1265 particles/m^3, in Asian water bodies - from 293 to 19860 particles/m^3 (Sarijan et al., 2021). MP in these reservoirs is represented mainly by fibers and also fragments, films and foams made of polypropylene (PP), polyethylene (PE), and polystyrene (PS) (Sarijan et al., 2021). Despite the removal of MP using various technological processes of water purification, it nevertheless could be detected in tap water. In the study of 159 samples of tap water obtained from various regions of the world, MP was detected in 81% of the samples; on average, its content was 5.45 particles/liter (Kosuth, Mason & Wattenberg, 2018).

MP is present in soil environments including farmlands, greenhouses, home gardens, coastal, industrial and floodplain soils (Hirt & Body-Malapel, 2020). In agricultural soils, the main causes of MP pollution are the introduction of solid biological substances and compost, irrigation with sewage water, mulch film, polymer fertilizers and pesticides, as well as atmospheric deposition (Kumar et al., 2020). In Sweden, up to 55.5 mg/kg or 593 particles/kg of MP is detected in floodplain soils (Scheurer & Bigalke, 2018). Plastics in soils are mainly represented by PE, PP, PS, PVC (Kumar et al., 2020).

In addition, MP particles are detected in the air. The average deposition rates of MP particles in urban and suburban areas in Paris are approximately 110±96 and 53±38 MP particles per m^2/day, respectively (Dris et al., 2016). In the city of Dongguan (China), this index is 36±7 particles per m^2/day (Cai et al., 2017), and in the center of London - 771±167 particles per m^2/day (Wright et al., 2020). MP is represented mainly by acrylic fibers with a thickness of 5-75 microns and a length of 250-2500 microns, as well as non-fibrillar parts of polyethylene (PE), polypropylene (PP), polystyrene (PS) with a size of 50-350 microns (Wright et al., 2020). In the atmosphere, MP fibers appear as a result of deterioration of textiles, non-fibrous particles are fragments of packaging materials. Fragments of worn-out automobile tires, particles of automobile and building paints, as well as emissions from industrial enterprises are also sources of MP in the atmosphere (Wright et al., 2020).

Microplastics in food chains and human food

Due to the progressive intensive pollution of all habitats by MP, it is often detected in animals. MP uptake can be direct or indirect - by transmission along the food chain (Smith et al., 2018). First of all, MP is accumulated in the bodies of biofilters - mollusks and zooplankton. It was found that the number of MP particles in soft tissues of blue mussels and giant Pacific oysters is 36±7 and 47±16 particles/100 g, respectively, and in the gastrointestinal tract of fish, the MP content averages 35 particles per fish (Van Cauwenberghe & Janssen, 2014; Kwon et al., 2020).

MP is detected in terrestrial food chains. MP were revealed in chicken stomachs (5.1 particles/g) and in feces (105 kg/g) (Huerta Lwanga et al., 2017), as well as in sheep feces (1000 particles/g) (Beriot et al., 2021).

An individual receives MP with water and food, and also inhales with air. It was demonstrated that MP particles could be found in sugar (0.44 particles/g), honey (0.10 particles/g), salt (0.11 particles/g), alcohol (32.27 particles/L), bottled water (94.37 particles/L), tap water (4.23 particles/L), and inhaled air (9.80 particles/m^3) (Cox et al., 2019; Yee et al., 2021). According to Danopoulus et al. (2020) estimates, a high content of MP was observed in seafood: a person consumes up to 27,825 particles of MP with shellfish, up to 17,716 particles with crustaceans and up to 8,323 particles with fish per year and the total maximum annual consumption of MP from all categories of seafood can reach 53,864 particles.

According to Kwon et al. (2020) more than 50% of the MP revealed in food is polyethylene (PE), polypropylene (PP), polystyrene (PS) and polyethylene terephthalate (PET). Particles in the form of fibers, including thin "filaments" were predominating. Fibers are considered to cause toxic effects at lower doses than spherical particles (Kwon et al., 2020).

As estimated by Cox et al. (2019), on average, a person consumes from 39,000 to 52,000 MP particles per year. If we add respirable plastic particles to this, the total number of plastics entering the human body reaches 74,000-121,000 particles per year (Yee et al., 2021). However, evaluation of MP particles number entering human body is indirect and very approximate, therefore this problem requires further research.

MP particles were detected in human feces: an average of 20 particles plastic 50-500 μm in size per 10 g, represented mainly by polypropylene (PP) and polyethylene terephthalate (PETE) (Schwabl et al., 2019). In addition, single plastic microparticles were found in the women placenta (Ragusa et al., 2021).

Effects of microplastics on animals

Invertebrates

The effects of MP exposure are characterized in details on aquatic organisms. In the review Haegerbaeumer et al. (2019) the detailed analysis of studies on the impact of MP on benthic marine and freshwater invertebrates presented: annelids, arthropods, ascidians, sea urchins, bivalve mollusks, rotifers. Based on 28 studies that assessed the MP effect on mortality, only 3 revealed significant changes: mortality increased in polychaetas *Perinereis aibuhitensis* (PS ø 8-12 μm, 100-1000 particles/ml), in shrimps *Palaemonetes pugio* (PE, PS, PP ø 30-165 μm, 50,000 particles/L) and in copepods *Tigriotopus japonicus* (PS ø 0.05 µm, 1.25 µg/L). Under the influence of MP, invertebrates demonstrated the decrease in food activity and fertility, a slowdown in larvae growth and development, an increase in oxygen consumption and production of its active forms, etc. However, due to the fact that the types, sizes and concentrations of MP particles are significantly different among articles, and different types of animals are used, comparison and analysis of MP effects are difficult.

Fishes

Microplastics was found in 49% of the examined fish from the North East Atlantic Ocean (*Dicentrachus labrax, Trachurus trachurus, Scomber colias*). 35% of the fish have microplastics in the gastrointestinal tract (mean±SD=1.2±2.0 items/individual), 36% had microplastics in the gills (0.7±1.2 items/individual) and 32% had microplastics in the dorsal muscle (0.054±0.099 items/g of tissue). MP particles are mainly represented by fibers in the size range 151-1500 microns and fragments in the size range 100-1500 microns of polyethylene and polyester. MP in fish causes an increase in the level of lipid peroxidation in the brain, gills and spinal muscles, as well as the increase in activity of brain acetylcholinesterase (Barboza et al., 2019).

Yong, Valiyaveetill & Tang (2020) conducted a meta-analysis of experimental studies that revealed significant signs of toxic or pathological effects of MP on fish. Toxic reactions generally arise from smaller particles, up to 5 µm, and polystyrene (PS) particles of 100 µm or larger do not have any significant effect. As a rule, MP particles are added to water containing fish and caviar ripening, concentrations vary from 1 to 1000 mg/L, most often 20 mg/L is used. The exposure time varies from several hours to several months, most often the exposure is 1 week. MP consumption can lead to disturbances in feeding behavior and motor activity in adults and fry, as well as to a decrease in fertility. There is evidence of the transmission of MP from mother to offspring (Pitt et al., 2018 (a)) and that prenatal exposure of MP affects the early fry development (Wang et al., 2019). With the increase in MP dose, MP accumulation in tissues and the severity of histological and biochemical changes increased (Lu et al., 2016; Wang et al., 2019; Pannetier et al., 2020).

Most studies of the MP effects on fish have been performed on zebrafish using polystyrene (PS) or, less commonly, polyethylene (PE) particles. PS particles 25-70 nm in size are able to penetrate the caviar shell, accumulate in the yolk sac, and move to the gastrointestinal tract. In embryos and fish fry, nanoparticles are found in the intestines, gallbladder, liver, pancreas, heart and brain. Transfer of PS NP from mother to offspring was revealed. According to various data, NP cause hyperactivity or, on the contrary, suppression of the fry motor activity, an increase in cortisol levels, a decrease in glucose levels, an increase in heart rate, inflammatory changes and fatty degeneration in the liver. NP affect the antioxidant system (the activity of glutathione reductase in the brain, muscles and testes of adult fish and their offspring decreases), transmission of nerve impulses (inhibition of acetylcholinesterase activity), expression of cytoskeleton genes (Lu et al., 2016; Chen et al., 2017; Pitt et al., 2018a; Pitt et al., 2018b; Brun et al., 2019).

PS particles with 5 μm diameter were detected in the gills, intestines and liver of fry and adult fish, caused fatty degeneration of hepatocytes and inflammatory changes in the liver and intestines, changes in the qualitative and quantitative composition of the intestinal microbiome, disturbances in the metabolism of carbohydrates and lipids, oxidative stress - changes in gene expression, associated with antioxidant protection (Lu et al., 2016; Qiao et al., 2019; Wan et al., 2019).

Larger particles of PS and PE, with diameter 10–90 μm, accumulated in the intestines of fry and adult fish and in the gills of adults. These particles caused changes in fish behavior and intestinal microbiome changes, increased the infiltration of the intestinal mucosa and gills by neutrophils, disturbed the metabolism of lipids, carbohydrates, amino acids and nucleic acids, affected the antioxidant defense, reduced fry after hatching survival rate, suppressed the expression of genes involved in the development and functioning of the fry nervous system (Lu et al., 2016; LeMoine et al., 2018; Limonta et al., 2019; Mak, Yeung & Chan, 2019; Malafaia et al., 2019; Wan et al., 2019).

The second most popular research object among fish are rice fish or Orasia *(Oryzias latipes* and *Oryzias melastigma*). After PS particles with a diameter of 0.05, 10 μm or MP samples collected on the beach exposure, they demonstrated the MP particles accumulation in gills, intestines and liver, increased mortality and a decrease in the average length and weight of fry and adult fish, oxidative stress and structural tissues damage where MP was accumulated, an increase in reactive oxygen species (ROS) levels and changes in the activity of antioxidant enzymes, dysfunctions of the reproductive system, and the decrease in caviar production. Prenatal exposure to MP affected early offspring development (Cong et al., 2019; Wang et al., 2019; Zhu et al., 2019; Pannetier et al., 2020).

In experiments on representatives from other fish species (crucian carp, carp, tilapia, catfish, perch, dorada, minnow) MP (PS 0.025-15 μm; PE 40-100 μm, PVC 40-200 μm) was detected in the intestines, gills, liver and brain. It caused changes in feeding behavior, shallow water behavior, a decrease in fish swimming speed and in range of movement, and slowed down fry growth. Metabolic disorders, increased oxygen consumption and excretion of ammonia, changes in the activity of liver enzymes, oxidative stress, structural damage in the liver, gills, intestines, skin and muscles were observed; suppression of acetylcholinesterase activity in the brain. Changes in the genes expression of the reproductive axis were revealed (Yong, Valiyaveetill & Tang, 2020).

Thus, in fish, MP accumulates mainly in the intestine, and in some cases, in the gills and liver, and pathological changes are detected in these tissues. In the gut, changes in gene expression and protein production associated with the integrity of the epithelial barrier, inflammation and oxidative stress, as well as changes in the gut microbiota were described. Disorders of lipid and carbohydrate metabolism, oxidative stress were discovered in the liver (fig.1).

MP enhances the toxic effects of a number of pollutants/toxic substances in fish, including phenanthrene (Karami et al., 2016), mercury (Barboza et al., 2018), cadmium (Lu et al., 2018a;

Banaee et al., 2019; Miranda, Vieira & Guilhermino, 2019), polychlorinated biphenyls (PCBs) (Rainieri et al., 2018), gold ions (Lee et al., 2019), as well as antibiotics (Zhang et al., 2019; Yong, Valiyaveetill & Tang, 2020).

Mammals

Studies of the MP effects on terrestrial mammals' organism were presented in the PubMed and Scopus databases by 30 papers on the effect of MP particles on laboratory mice and rats. Moreover, the earliest of them was published in 2017, and half of the works were published in 2021, which indicates the growing interest of the scientific community towards this problem.

The species and lines of animals, the doses, type and particle size of MP and the methods of its administration, the duration of exposure in the investigations vary considerably (Table 1). Most of the studies (24 articles) were carried out on mice, mainly on nonlinear ICR (CD-1) and C57Bl/6 lines, less often on Balb/c and Swiss; 6 studies were performed in Wistar and Sprague-Dawley rats. In most studies (13 studies each), animals received MP per orally with water from a drinking bowl or through a gastric tube. In a few studies, MP was administrated through the food, injected intraperitoneally, by inhalation or intratracheal administration. Polystyrene particles (PS, 25 studies) with a diameter of 0.02 to 500 μm (median 4.5 μm) were predominantly used, less often polyethylene particles (PE, 6 studies) 0.4-150 μm (average 35 μm) size.

Doses for oral exposure vary from 0.01 to 100 mg MP per kg of body weight per day. Most often the daily doses of MP were 0.024 and 0.24 mg/kg when MP was added in drinking bowl; 4 and 20-60 mg/kg when administered through a gastric tube, and in experiments with rats - about 0.05, 0.5 and 5 mg/kg. In terms of the number of MP particles per kg of animal body weight per day, the doses ranged from 3.5×10^3 to 1.5×10^{14}, and the median was 2.5×10^8 particles/kg/day. According to Cox et al. (2019), a person consumes approximately 39000 to 52000 particles/year with water and food, i.e., about 1.5-2 particles/kg/day. The concentration of MP in water varied from 7.2×10^3 to 1.2×10^{18} particles /m^3, the median was 1.2×10^{11} particles /m^3, in experiments on mice and rats, which were drink water with MP. MP concentration in marine and fresh water ranges from 0.1 to 2×10^4 particles/m^3 (Erni-Cassola G et al., 2019; Sarijan S et al., 2021). Thus, MP concentrations used in experiments on mice and rats are, on average, million times higher than its content in natural waters and in human consumption.

The duration varied from a single injection of MP to continuous exposure over 3 months, most often 4 weeks were indicated. Such a variety of models makes it much more difficult to compare the obtained data.

In case of oral administration, MP primarily acted on the gastrointestinal tract. A number of studies demonstrated that polystyrene (PS) with a diameter of 0.5-50 μm accumulated in the colon of mice, caused damage to the colon epithelial barrier, a decrease in mucus production, a decrease in the expression of tight-junction proteins, and changes in the intestinal microflora composition (Lu et al., 2018b; Jin et al., 2019; Li et al., 2020a; Qiao et al., 2021). MP was detected in the rodents' liver and kidneys, where it caused inflammatory changes and oxidative stress, a decrease in the liver relative mass, impaired energy and lipid metabolism (Deng et al., 2017; Deng et al., 2018; Yang et al., 2019; Deng et al., 2021; Wang et al., 2021). MP due to the induction of oxidative stress and damage to mitochondria could cause the death of cardiomyocytes, the development of cardiac fibrosis and impairment of its function (Li et al., 2020b; Wei et al., 2021). When mice were administrated with MP, violations of skeletal muscle regeneration, myosatellite cells suppression of myogenic and stimulation of adipogenic differentiation were observed (Shengchen et al., 2021). MP affected hematopoiesis: it suppressed the leukocytes development and changed the expression of dozen genes in bone marrow cells (Sun et al., 2021). MP caused cognitive impairment and affected animal behavior (da Costa Araújo & Malafaia, 2021; Estrela et al., 2021). In addition, MP affected reproductive function and also caused developmental disorders in offspring. In male mice, MP penetrated the testes, caused damage of the seminiferous tubule's epithelium, forced apoptosis of spermatogenic cells, while the testosterone level, the number and motility of spermatozoids decrease with an increase in the number of deformed spermatozoids (Xie et al., 2020; Hou et al., 2021a; Jin et al., 2021; Li et al., 2021). In females, MP penetrated the ovaries, causes the death of granulosa cells and fibrosis (An et al., 2021; Hou et al., 2021b). In the offspring of mice that consumed plastic, the body weight was reduced, the mortality rate was higher in the first day after birth, metabolic disorders, changes in the intestinal microflora composition were revealed (Luo et al., 2019a; Luo et al., 2019b; Park et al., 2020). MP enhanced the toxic and pathological effects of organophosphate antiperenes, phthalates and sodium dextran sulfate (Deng et al., 2018; Deng et al., 2020; Deng et al., 2021; Zheng et al., 2021).

Two studies evaluated the effects of MP entering the airways as a result of inhalation or intratracheal administration. MP caused the increase in the relative mass of the heart, a decrease in the number of leukocytes and lymphocytes in blood, a decrease in the time of inspiration. There was observed a tendency to the increase in the content of TGF-β and TNF-α cytokines in the lung. It was demonstrated that MP particles were transmitted from mother to fetus: MP was detected in the placenta, as well as in the liver, lungs, heart, kidneys, and brain in embryos (Fournier et al., 2020; Lim et al., 2021).

However, some studies didn't reveal any significant effects of microplastics exposure. According to Stok et al. (2019) in mice treated with MP, body and organ weight did not change, and there were no signs of inflammation or oxidative stress in the intestine. Rafiee et al. (2018) found no changes in the results of neurobehavioral tests in rats that consumed MP.

Thus, in experiments on laboratory rodents, it was demonstrated that MP, entering the body with water, food, and air, could spread to various organs and tissues. MP was detected in the intestines, liver, kidneys, lungs, spleen, heart, ovaries and testes of animals, causing biochemical changes, structural damage and dysfunction of these organs. MP could penetrate through the placenta into developing fetuses and affect the offspring development. In addition, MP could carry and enhance the negative effects of various pollutants (fig.2). However, due to the small number of studies and the significantly varying doses, sizes of the MP and the duration of exposure, the studied parameters, the data obtained were fragmentary and contradictory. In addition, the doses of MP used in most experiments significantly exceed the content of MP in natural sources and in consumption by humans.

Conclusions

Every year, million tons of plastic waste are generated around the world. Less than a quarter from this volume is recycled and disposed of. Plastic waste broken into small particles of MP, which carried by water and wind. Due to the pollution of all habitats, particles of microplastics with food, water and inhaled air penetrate and accumulate in the bodies of various living organisms, including human. Experimental studies on invertebrates, fish, mice and rats show that microplastics can provide negative effects on health by causing pathological changes in various organs. In accordance with the above, environmental pollution by microplastics can pose a threat to human health. However, the data obtained are ambiguous and fragmented. Some parameters of microplastics that can influence its effects, such as transport of sorbed contaminants or pathogens on the plastic particles and the degradation stage of the plastic, have not been studied. Therefore, further research in this area is required.

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Figure 1. Effects of microplastics on fishes

Figure 2. Effects of microplastics on mice and rats

Figure 1

Figure 1. Effects of microplastics on fishes

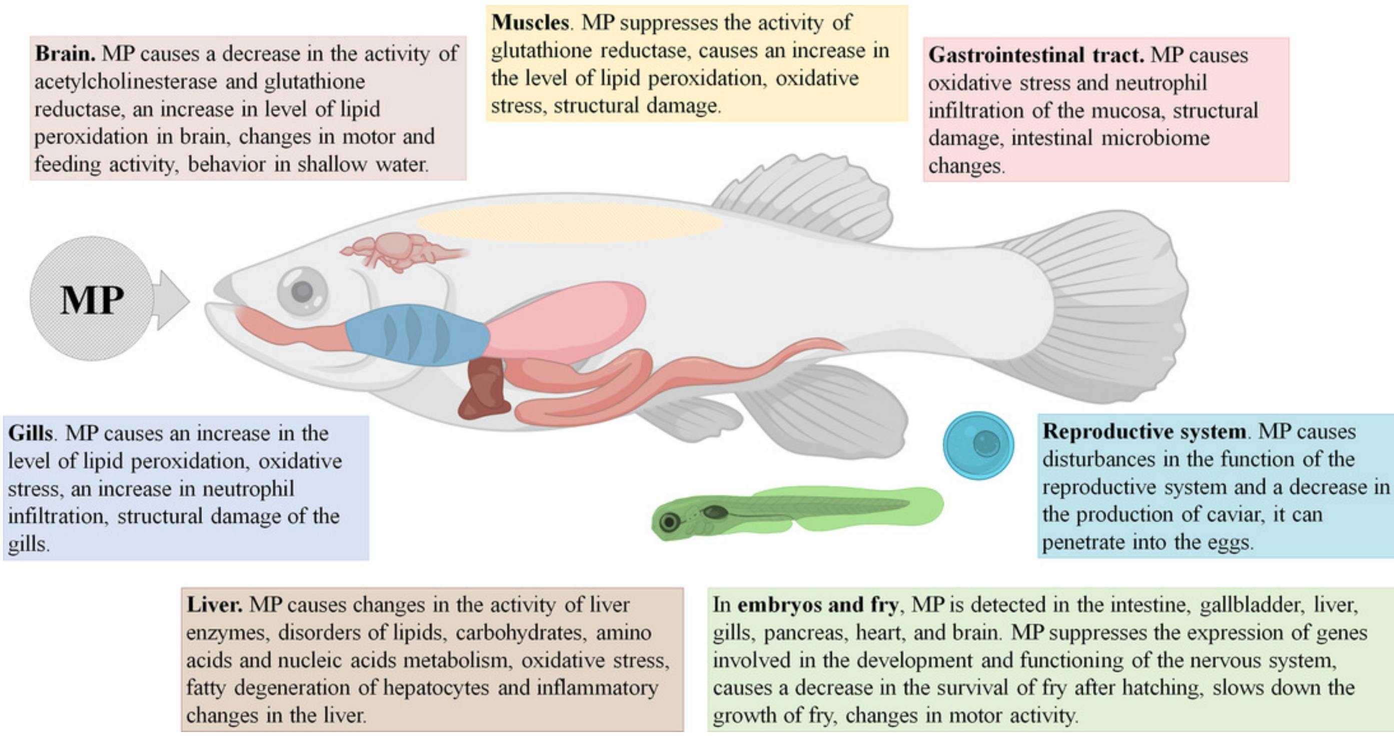

Figure 2

Figure 2. Effects of microplastics on mice and rats

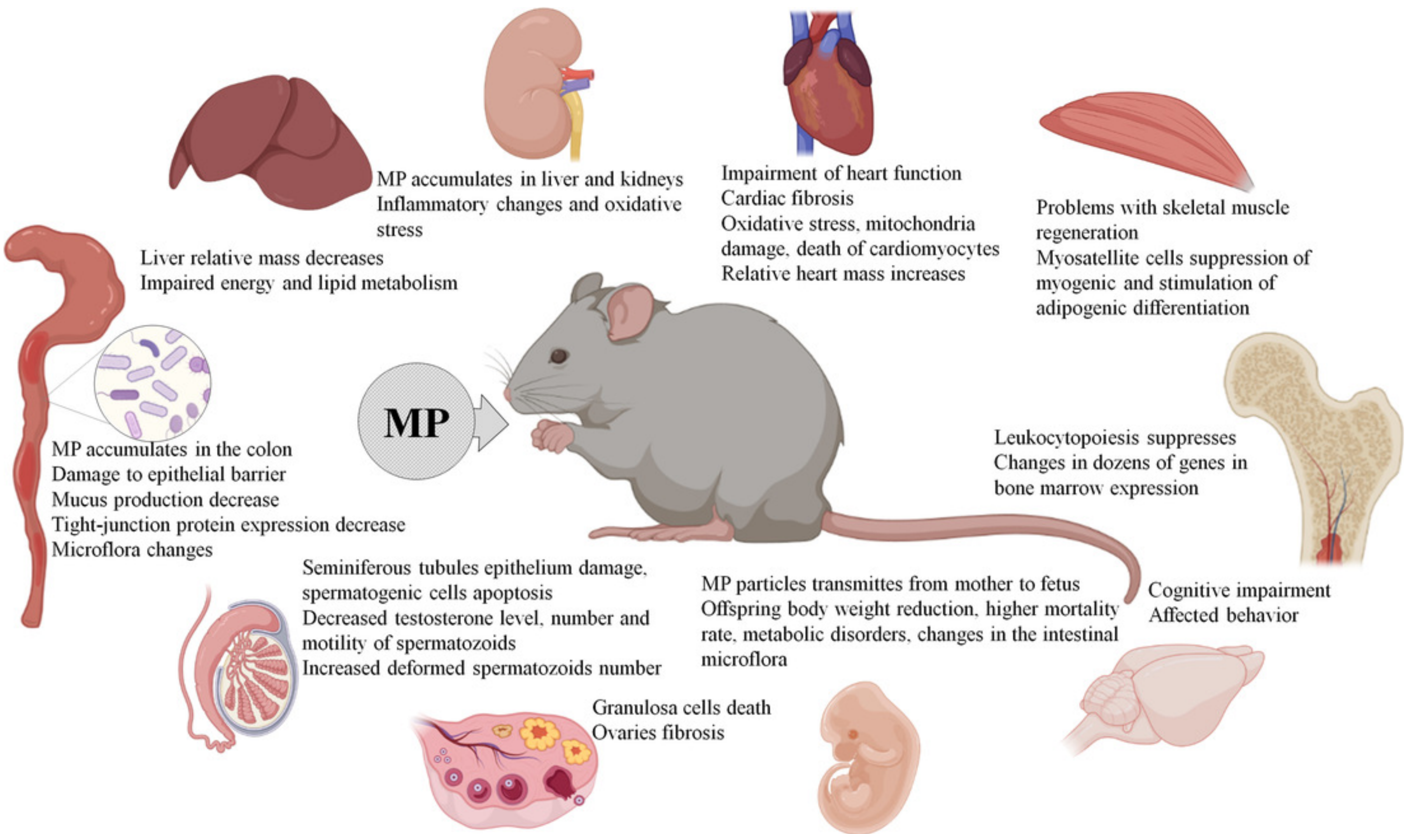

Table 1(on next page)

Experimental researches of the effect of microplastic (MP) on the health of laboratory rodents

*In articles, when MP is added to drinkers, as a rule, the concentration of MP in drinkers is indicated as mg/l, when administered through a gastric tube - the amount of MP (mg) per animal. We recalculated the MP dose as mg of MP per kg of animal's weight per day, taking the average weight of a mouse equal to 25 g, a rat - 250 g, daily water consumption in a mouse - 6 ml, in a rat - 25 ml. NP – nanoplastic

Table 1:

Experimental researches of the effect of microplastic (MP) on the health of laboratory rodents

Publication	Animals	Type and size of MP particles, additional treatment	Dose*	Exposure	The results of the impact of MP
Replacing water in drinkers with MP suspension					
Luo T et al., 2019(b)	Pregnant female ICR mice	PS 0.5 µm and 5 µm	0.024 and 0.24 mg/kg/day	Throughout the entire pregnancy (3 weeks)	Disorders of fatty acid metabolism were observed in the offspring of mice that consumed MPs.
Lu L et al., 2018(b)	Male ICR mice	PS 0.5 µm and 50 µm	0.024 and 0.24 mg/kg/day	5 weeks	MP causes a decrease in body weight, the relative mass of the liver and adipose tissue; decreased mucin secretion and expression of Muc1 and Klf4 in the colon; significant changes in the composition of the intestinal microflora; disorders of lipid metabolism in the liver.
Hou B et al., 2021	Male ICR mice	PS 5 µm	0.024, 0.24 and 2.4 mg/kg/day	5 weeks	Under the influence of MP, there was the decrease in the number of viable spermatozoa in the epididymis, an increase in the proportion of deformed spermatozoa, atrophy and apoptosis of spermatozoa in the testes, an increase in the expression of pro-inflammatory markers: NF-κB, IL-1β, IL-6, a decrease in the expression of the anti-inflammatory molecule Nrf2/HO-1.
Jin Y et al., 2019	Male ICR mice	PS 5 µm	0.024 and 0.24 mg/kg/day	6 weeks	MP accumulates in the intestine, causes a disturbance of the intestinal barrier, changes in the intestinal microflora, disturbances in the metabolism of bile acids.
Luo T et al., 2019(a)	Pregnant female ICR mice	PS 5 µm	0.024 and 0.24 mg/kg/day	Throughout the pregnancy and lactation (6 weeks)	In the offspring of mice that received MP during gestation and feeding, metabolic disorders in the liver and changes in the composition of the intestinal microflora are detected.
Shengchen W et al., 2021	Male C57BL/6 mice	PS 1-10 µm and 50-100 µm	2.4 mg/kg/day	8 weeks (On the 25th day, the tibialis anterior muscle was injured by the injection of BaCl2, 30 days after the muscle injury animals were withdrawn from the experiment)	MP consumption led to overproduction of ROS, the development of oxidative stress, and impaired skeletal muscle regeneration. MP suppressed myogenic and stimulated adipogenic differentiation of myosatellite cells. Muscle regeneration was negatively correlated with MP particle size.

Zheng H et al., 2021	Male C57 mice	PS 5 µm, induction of acute ulcerative colitis with 3% sodium dextran sulfate (DSS) solution in drinkers	0.12 mg/kg/day	7 days	MP exacerbates the DSS-induced acute colitis; causes dystrophic changes in the liver.
Deng Y et al., 2018	Male CD-1 mice	PS and PE 0.5–1 µm contaminated with organophosphate fire retardants (OPFR)	0.48 mg/kg/day	13 weeks	MP and OPFR together exhibited more pronounced effects than either separately: oxidative stress, neurotoxicity, impaired amino acid metabolism and energy metabolism.
An R et al., 2021	Female Wistar rats	PS 0.5 µm	0.06, 0.6 and 6 mg/kg/day	13 weeks	MP is detected in ovarian granulosa cells, causes their apoptosis and the development of ovarian fibrosis.
Hou J et al., 2021	Female Wistar rats	PS 0.5 µm	0.015; 0.15 and 1.5 mg/kg/day	13 weeks	MP is detected in ovarian granulosa cells, causes pyroptosis and apoptosis of these cells.
Li S et al., 2021	Female Wistar rats	PS 0.5 µm	0.06, 0.6 and 6 mg/kg/day	13 weeks	MP causes damage to the seminiferous tubules, apoptosis of spermatogenic cells, a decrease in sperm motility, an increase in the proportion of abnormal spermatozoa.
Li Z et al., 2020	Female Wistar rats	PS 0.5 µm	0.05, 0.5 and 5 mg/kg/day	13 weeks	MP causes oxidative stress in the myocardium, apoptosis of cardiomyocytes, cardiosclerosis and cardiac dysfunction.
Wei J et al., 2021	Female Wistar rats	PS 500 µm	0.05, 0.5 and 5 mg/kg/day	13 weeks	MP consumption leads to disruption of the structure and function of the heart. Damage of mitochondria in cardiomyocytes and death of these cells are noted. Levels of creatine kinase-MB and cardiac troponin I (cTnI) are elevated.
Administration of MP suspension through a gastric tube					
Qiao J et al., 2021	Male C57/B6 mice	PS 0.07 µm (NP) and 5 µm, unmodified, negatively charged carboxylated and positively charged aminated	0.2 and 2 mg/kg/day	4 weeks	MP caused intestinal damage, a decrease in the expression of tight contact proteins in the intestinal epithelium, and pronounced changes in the intestinal microflora.
Jin H et al., 2021	Male Balb/c mice	PS 0.5 µm, 4 µm and 10 µm	40 mg/kg/day	4 weeks	MP particles, 4 and 10 µm in diameter, are detected in the testes one day after the first injection. On the 28th day of exposure, a decrease in testosterone levels and sperm quality is observed. Spermatogenic cells die and are arranged randomly, multinucleated gonocytes appear in the seminiferous tubules.

Stock V et al., 2019	Male genetically modified C57BL/6 mice	PS 1 µm, 4 µm and 10 µm	1, 63 and 33 mg/kg/day according to size	4 weeks	In animals getting MP, body and organ weight did not change, there were no signs of oxidative stress or inflammation in the intestine.
Wang YL et al., 2021	Male C57BL/6 mice	PS 2 µm	8 and 16 mg/kg twice a week	4 or 8 weeks	MP accumulates in the kidneys, causing structural damage. In the kidney, levels of ER stress, the production of inflammatory markers and proteins associated with autophagy are increased.
Sun R et al., 2021	Male C57BL/6 mice	PS 5 µm	4 and 20 mg/kg/day	4 weeks	MP affects hematopoiesis. Decreases the number of leukocytes and the CFU-GM, CFU-M, CFU-G; changes 41 (lower dose) or 32 (large dose) genes in bone marrow cells.
Deng Y et al., 2017	Male ICR mice	PS 5 µm and 20 µm	4 mg/kg/day	4 weeks	The maximum concentration of MP in the liver, kidneys, and intestines is reached by the 14th day of the experiment. The relative weight of the liver decreases at a MP dose of 0.5 mg/day. In the liver, inflammatory changes and fatty degeneration are observed. Disorders of energy and lipid metabolism, oxidative stress were revealed.
Yang YF et al., 2019	Male mice	PS 5 µm and 20 µm	0.4, 4 and 20 mg/kg/day	4 weeks	Toxicokinetic/toxicodynamic study of MP influence. The accumulation of MPs in the liver, kidneys, and intestines was assessed over time.
Xie X et al., 2020	Male Balb/c mice	PS 5–5.9 µm	0.4; 4 and 40 mg/kg/day	6 weeks	MP causes a decrease in spermatozoa number and mobility, an increase in the proportion of deformed spermatozoa; a decrease in the activity of the enzymes succinate dehydrogenase and lactate dehydrogenase; decrease in testosterone content, development of oxidative stress.
Rafiee M et al., 2018	Male Wistar rats	PS 0.025 µm and 0.05 µm (NP)	1, 3, 6 or 10 mg/kg/day	5 weeks	In neurobehavioral tests, statistically significant changes were not observed upon exposure to MP, body weight did not change.
da Costa Araújo AP, Malafaia G, 2021	Male Swiss mice	PE 35,46 ± 18,17 µm	4.8 mg/kg/day	1 week	In animals that consumed MP, a decrease in locomotor activity and a higher anxiety index in the open field test, a lack of protective social aggregation, and behavior with a reduced risk assessment when meeting a potential predator were observed.

Park EJ et al., 2020	Male and female ICR mice	PE 40-48 μm modified with acid and hydroxy groups	3.75, 15 and 60 mg/kg/day	13 weeks	MP caused reactions from the immune system in adult animals: in mice of both sexes, the content of neutrophils in blood increased, in females, the content of IgA in blood increased, and the subpopulation composition of lymphocytes in the spleen changed. In animals receiving MP, the number of live births per female and the body weight of newborn pups decreased significantly.
Deng Y et al., 2021	Male CD-1 mice	PE 0.4–5 μm, phthalate-contaminated	100 mg/kg/day	4 weeks	MP can penetrate the testes of mice. MPs with phthalates accumulate in the liver, intestines, and testes. MP enhances the reproductive toxicity of phthalates.
Deng Y et al., 2020	Male CD-1 mice	PE 45-53 μm, phthalate-contaminated	100 mg/kg/day	4 weeks	MP can transport and release phthalates into the intestines of mice. MP enhances the toxic effects of phthalates: increased intestinal permeability, oxidative stress, inflammatory reactions, metabolic disorders.
MP in food					
Li B et al., 2020	Male C57BL/6 mice	PE 10–150 μm	0.24, 2.4 and 24 mg/kg/day	5 weeks	MP caused changes in the composition and diversity of intestinal microflora, an increase in the level of IL-1α in the blood serum, an increase in the proportion of Th17 and Treg cells among CD4+ cells. MP in a high dose caused the development of inflammation in the small intestine.
Intratracheal introduction of MP					
Fournier SB et al., 2020	Pregnant female Sprague Dawley rats	PS 0.02 μm (NP)	2.64×10^{14} MP particles	1 time on day 19 of gestation, removal from the experiment in a day	MP particles were detected in maternal lungs, heart and spleen. MP was detected in the placenta, as well as in the liver, lungs, heart, kidneys and brain of fetuses, which indicates translocation of MPs from the mother's lungs to the fetal tissue in late pregnancy.
MP inhalation					
Lim D et al., 2021	Male and female Sprague-Dawley rats	PS 0.1 μm (NP)	MP air concentration 0.75×10^5, 1.5×10^5 and 3×10^5 particles/sm^3	2 weeks	Under the influence of MP, the increase in the relative mass of the heart, a decrease in the content of leukocytes and lymphocytes in the blood, a decrease in the time of inspiration were revealed, furthermore a tendency to an increase in the content of cytokines TGF-β and TNF-α in the lung tissue was observed.
Intraperitoneal injection of MP					
Estrela FN et al., 2021	Male Swiss mice	PS 0.023 μm (NP)	14.6 ng/kg	3 days	MP causes cognitive impairments, violations of the redox balance, and a decrease in the activity of acetylcholinesterase in the brain.

*In articles, when MP is added to drinkers, as a rule, the concentration of MP in drinkers is indicated as mg/l, when administered through a gastric tube - the amount of MP (mg) per animal. We recalculated the MP dose as mg of MP per kg of animal's weight per day, taking the average weight of a mouse equal to 25 g, a rat - 250 g, daily water consumption in a mouse - 6 ml, in a rat - 25 ml.

NP – nanoplastic