Microplastics and Nanoplastics on Livestock Health

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Pollution due to microplastics and nanoplastics is one of the major environmental issues and represents a growing threat to human and animal health. In aquatic species, there is a large amount of information regarding the perturbation of marine organisms; only few studies focused on the pathophysiological consequences of an acute and chronic exposure to micro- and nanoplastics in mammalian systems, especially on the reproductive system.

Keywords: microplastics ; nanoplastics ; reproductive system ; health ; livestock

1. Introduction

Plastics have been widely used in production and life ever since their invention due to their remarkable properties of durability, lightness, stability and low cost. The production of plastic per year has increased tremendously worldwide, reached 390 million tons in 2021 compared to only 2 million tons produced in 1950 [1]. The demand for plastics in Europe reached 50.7 million tons, with Germany in the lead (24.2%) and Italy in second (13.8%). One of the largest end use markets is the packaging and building/construction industries. While plastics in the building and construction sector are functional for 35 years, some plastics, especially in the packaging industry, might have very short lifetimes of 6 months or are single-use only, thus contributing to the immense waste management issue. It is noteworthy that the COVID-19 pandemic has increased the plastic use and environmental contamination by plastic as a result of the common use of masks, gloves and other plastic consumables.

The main characteristics of plastics are hardness, resistance to stress and impact, elasticity, machinability and economical cost. Plastic is a macromolecular material composed of polymers of different lengths. The most common compounds used to make plastics are polyethylene (PE), polypropylene (PP), polystyrene (PS), polyethylene terephthalate (PET) and polyvinyl chloride (PVC). Furthermore, various additives such as plasticizers, flame retardants, stabilizers, colorants, antistatic agents, lubricants, etc. are used to enhance their performance [2]. Commonly used additives are phthalate esters and bisphenol A (BPA). Phthalate esters serve to make PVC more flexible and softer [3], and BPA is used because of its translucent property, to increase the mechanical and thermal resistance [4].

In general, plastic particles can be divided into two categories: primary particles, which are intentionally produced by the industry for various purposes (pellets used to make plastic products, abrasive microbeads or personal health care products), while secondary particles are generated through disintegration or abrasion of materials or waste released into the environment (washing synthetic clothes, tire abrasion, etc.) [5]. The exposure of plastic waste to physical, mechanical, chemical and biological processes such as fragmentation, weathering, hydrolysis, UV radiation and biodegradation leads to the production of microplastics (<5 mm, MPs) and nanoplastics (<0.1 µm, NPs). Plastic residues persist in the environment, especially in marine and aquatic ecosystems; it is estimated that more than 68% of these residues in the oceans originate from the fragmentation of waste that is not disposed of or improperly recycled. Not to be underestimated are the biodegradable plastics, which presence in the environment is increasing due to incomplete biodegradability and increasing use [6][7]. The ecotoxicological effects of MPs/NPs on marine phytoplanktons and zooplanktons, invertebrates and plants are well documented, while ingestion and accumulation from marine prey, leading to transfer to the predators, also occur [8][9]. The distribution of plastics is ubiquitous in the environment and includes atmosphere, soil and water; this likely represents a potential entry of microplastics into the food chain and, therefore, a concern for human and animal health.

The three main routes by which microplastics and nanoplastics can enter the human and mammalian body are the (1) ingestion of contaminated food and water supplies, (2) inhalation of airborne plastic particles originating from synthetic textiles and polluted outdoor air and (3) skin contact, with these plastic particles passing through the skin barrier [6]. In addition, due to their chemical–physical properties, these materials may facilitate the binding and transport of chemical contaminants (e.g., antibiotics and heavy metals) and microbial agents (e.g., bacteria), thus increasing their impact on the environment and on human beings and animal health [10]. Several types of toxic chemicals have been reported to be

associated with MPs, most of which are either heavy metals (e.g., arsenic, zinc, copper, etc.); persistent organic pollutants (POPs), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs) and organic pesticides [11]. In addition, several microorganisms are able to bind to MPs, such as fungi, diatoms, algae and bacteria [10]. All microbial and chemical associations with MPs depend on various factors such as MP type and size, pH, salinity, plastic aging effect and polymer crystallinity [12]. Microplastics affect the evolution of microbial communities and increase gene exchanges, including antibiotic resistance genes (ARGs). There are no published findings on the abundance and diversity of ARGs in bacterial taxa in the marine plastic environment, although seawater has been identified as a global reservoir for ARGs and for metal resistance genes (MRGs) [13].

2. Mammalian Exposure to Micro- and Nanoplastics

2.1. Mammalian Exposure to Microplastics through Ingestion and Drinking Water

Animals ingest microplastics and nanoplastics because of their presence in water and in different feeds and forages. Firstly, microplastics are ubiquitous in surface water, groundwater and wastewater [5][14], with different types of plastics such as fragments, fibers, films, etc. Animals and humans drink water contaminated with MPs, also present in water used for the irrigation of fields [15][16].

In a recent report of World Health Organization's (WHO) on "Microplastic in drinking water", indicates that there is no yet proof of harm and calls for more research to be conducted, so there can be a greater understanding of the potential detrimental effects of microplastics in drink water [17].

There are many pathways for plastic particles to enter a soil environment such as agricultural plastic mulch film, the use of plastic-coated fertilizers, the application of biosolids, the airborne deposition and roadside littering. These nanoparticles can be absorbed via plant roots and transported through the xylem pathway to edible parts [18] of the plant that is intended for human or animal consumption and thus enter the food chain [19]. In some intensively cultivated areas of Europe, where ruminants graze after the harvesting of grains, the ingestion of plastic fragments occurs [20]. In Europe, 63,000-430,000 tons of MPs were estimated to be deposited on agricultural soils each year [21]. In developing countries, such as Ethiopia and India, however, the issue of plastic waste is even more widespread, because many animals, including livestock, are not maintained in confined areas and feed on garbage. When ingested, plastics slowly release chemicals in the rumen, which can enter the systemic bloodstream and contaminate milk and meat products and the food chain. These chemicals have adverse effects on human health [22][23].

Another risk is represented by the migration of additives or MPs from plastic packaging into solid animal feed [24], so researchers also must consider the techniques used to store food. The additives are found in PP and PE packaging and can migrate into solid feed of cows, with the risk of being transferred into milk, as reported by Russo et al. [25]. The results from another study by Zhou et al. [26] indicated that nonpackaged fresh meats, such as pork, chicken, beef and mutton, were contaminated with BPs.

Considering both humans and also other livestock species such as pigs and poultry, there should be a focus on the presence of MPs in fishmeal and fish oil, which are widely used as a nutritional source in food- producing animals feed [11][27].

In fish and mice, there is some information on pathological manifestations associated with the absorption of nanoplastics across the gastrointestinal wall. In mice, ingested MPs/NPs were detected in the intestine, liver and kidneys. In the gut, the plastics induced alterations such as a reduction in mucosal secretion, intestinal barrier dysfunction, inflammation and microbiota dysbiosis. In the liver, however, these particles led to inflammation and to subsequent alterations in the blood lipid profile. Based on these pathological outcomes in mice, it will be important to understand how the ingestion of nanoplastics may also affect food-producing animals.

Huerta Lwanga et al. [28] reported a possible trophic transfer of MPs from home gardens to earthworms and chickens. In chickens, MPs were recovered from the gizzard lumen and feces. It has been postulated that plastic ingestion led to a reduction in gizzard volume, which, in turn, decreased the foraging time and, hence, growth [29]. Zhang et al. [30], however, reported an estimate of MP intake ranging from 3 to 677 mg/week for domestic animals. Campanale et al. [31] reported that humans ingest about 80 g/day of microplastics through plants grown on polluted soil.

2.2. Mammalian Exposure to Microplastics through Inhalation

The second most likely route of exposure of mammals to MPs/NPs is through inhalation. Minute particles of plastic may be suspended in the air; they mainly originate from synthetic textiles, but also, the inhalation of dried wastewater fertilizer or atmospheric fallout occurs [32]. Air contaminated with MPs/NPs comes into direct contact with the respiratory tract, affecting different layers and cells. Considering the extremely fine structure of the alveolar surface, NPs may penetrate this tissue, thus entering the bloodstream and, subsequently, other body tissues [6]. In a cell culture of human alveolar epithelial cells, there were cytotoxic effects, oxidative stress responses and inflammatory responses against MPs.

2.3. Mammalian Exposure to Microplastics through Skin Contact

Another entrance pathway of MPs/NPs could be transdermal, more specifically by contact or injection. Plastic particles can pass through the skin with the use of health and beauty products or contact with contaminated water. The point of access for MPs/NPs could be the stratum corneum, but they could also transfer via the sweat glands, skin wounds or hair follicles [6]. The outermost layer of the skin, the stratum corneum, forms a natural barrier, making it unlikely that molecules will penetrate this tissue layer if in an intact state. Alvarez-Roman et al. [33], performed a study on the penetration of polystyrene particles ranging from 20 to 200 nm in diameter into the stratum corneum of pigs. Many 20 nm polystyrene NPs concentrated in the hair follicles of these pigs, even though the particles were not transferred into the inner layers, so there is only a superficial skin penetration of NPs. However, it cannot be excluded that these particles may enter the systemic circulation by means of plastic-based intravenous catheters, syringes and other drug delivery systems [34].

There has been elaboration on the current knowledge regarding the different entry routes of small plastic particles; however, the possible deposition and effects of these compounds in animals have yet to be resolved.

One thing is certain: once these compounds enter the body, there is not a ready clearance from the tissues. Rather, there is a presence of NPs in the blood and consequent transport via the blood circulation to all the tissues of the body [35].

3. Risks of Exposure to Microplastics and Nanoplastics in Food-Producing Animals

The risk posed by MPs and NPs to humans and animals is of physical, chemical and microbiological nature. Physical risks are due to the small sizes of MPs/NPs that can cross biological barriers such as the skin, gut, hemato–encephalic, testicular and even placental tissues and cause direct damage. The chemical risks are due to the presence of persistent additives or contaminants that are potentially hazardous, while the microbiological risks are related to microorganisms adhering to the MP surface [36].

The exposure of animals to MPs results in inflammation, cytotoxicity (e.g., oxidative stress, cells damage, cell viability and altered membrane function), genotoxicity (through oxidative damage) and immunotoxicity [37]. Many of the toxic effects of MPs are intricately interconnected, as perturbation of one process may trigger a cascade of other toxicological responses [38]. The toxicity, translocation and accumulation of MPs depend on their size, shape, dose, surface functionalization and charge, as well as hydrophobicity. There is convincing evidence that MPs accumulate in tissues. The results from many studies [5][6][17] are indicative that inflammation, oxidative stress, apoptosis, necrosis and immune responses occur because of the accumulation of MPs/NPs in human and animal tissues.

Particles < 100 µm in diameter can cross cell membranes, and particles < 20 µm can be efficiently translocated to various organs. Smaller particles can be absorbed systemically and may partially pass through tissue barriers, however the larger particles are excreted through feces. The blood–brain barrier, as well as the placental barrier, may be crossed by particles ranging from 0.1 to 10 µm in diameter, while passage through the gastrointestinal tissue walls can occur for MPs as large as 150 µm. Presumably, plastic particles smaller than 2.5 µm can also circulate systemically in the organism by endocytosis. Ragusa et al. [39] analyzed six human placentae, in four out of the six specimens, 12 MP fragments were observed. Furthermore, the particles were not only in the maternal side but also in the fetal side of the placenta and in the chorioamniotic membrane, thus highlighting a potential risk to the fetus. Wick et al. [40] also reported that polystyrene particles 240 nm in size can cross the placental barrier through diffusion or binding to cellular transport proteins. The accumulation of MPs primarily occurs in the liver, kidneys, gut [41], stomach, small intestine and mesenteric lymph nodes [34]. Fournier et al. [42] administered 0.02 µm polystyrene particles to late-gestation female rats and observed that the transfer of these particles to fetal tissues, including the liver, lungs, heart, kidneys and brain, occurred. This is indicative of the potential risks of the microplastics to the reproductive tract, as well as to the fetus, in all species.

The toxicological risk of microplastics and nanoplastics is increased due to the large amount of additives used in the production of these polymers. The most common and harmful additives are Bisphenol A and phthalate esters, including DEHP and MEHP [6]. These chemicals are cytotoxic and can also behave as endocrine disruptors (EDCs); therefore, alterations of the reproductive physiology of animals may occur as a result of the hormonal activity of these compounds [43]. In fact, EDCs are considered more harmful than MPs, since these compounds are responsible for the induction of cancer [41], mutations of DNA and toxic reproductive effects. Moreover, these chemicals are recalcitrant in the environment, can accumulate in the food chain and bodies and show harmful proprieties such as hormone disruptors [31]. It has been demonstrated that exposure of laboratory animals to MPs and their additives leads to the disruption of adipogenesis and lipid metabolism through the activation of peroxisome proliferation-activated receptors (PPARs), suggesting that MP exposure may be associated with the increasing prevalence of obesity globally [38].

4. Effects of Microplastics, Nanoplastics and their additives on Reproduction

The exposure of MPs/NPs may trigger toxicity pathways, including the exacerbation of inflammation and oxidative stress (OS). After being absorbed, MPs/NPs may have actions locally or be transported to the bloodstream and, after the translocation, may reach all organs and tissues, including the gonads. The NPs can also accumulate in several reproductive tissues, thus inducing reproductive dysfunction(s). Reproductive alterations are mainly mediated by oxidative stress and are also associated with the upregulation of prooxidant mediators (reactive oxygen species, lipids and DNA oxidation), cell death, proinflammatory molecular pathways and cytokines and the inhibition of enzymatic and nonenzymatic antioxidant defense mechanisms.

In mice female reproductive systems, the major microstructural abnormalities identified consisted of dilatation of the oviducts, presence of ovarian cysts, increased number of corpora lutea, decreased thickness of the granulosa layer in secondary follicles, reduced number of growing follicles, greater accumulation of ovarian collagen and fibronectin and apoptosis of granulosa cells [44]. Furthermore, MPs/NPs increase fibrotic processes in the ovaries and in granulosa cells by increasing the levels of ROS and MDA and decreasing the activities of antioxidant enzymes, including SOD, CAT and GPx [9].

In mice and rats male reproductive systems, MPs and NPs detection in the testes was associated with multiple microstructural alterations, including testicular atrophy, incomplete spermatogenesis, disorganization or disruption, as well as with increased permeability of the blood–testis barrier [43]. Concerning the male gametes, greater amounts of sperm abnormalities have been observed in association with the presence of MPs and NPs; the major defects consisted of head and tail alterations, as well as acrosome loss. Additionally, other seminal characteristics were affected and resulted in a lesser sperm motility or immobility, apoptosis and an overall lower sperm count [44][45].

Concerning embryonic development, it has been suggested [9] that MPs/NPs induce germ cell abnormalities by altering the fluidity of the membranes that are in contact with gametes, with the MPs not entering the embryo but adhering to the surface of the chorion and reducing the exchange of oxygen, followed by embryonic physiological disruption. Yin et al. [46], however, reported that NPs could be transported into the embryo and accumulate in the yolk sac, leading to alterations in nutrient absorption. Several studies in women confirm the presence of MPs in the fetal and maternal placenta and chorionic membranes which might be detrimental to fetal development [9][39][40]. The results from other studies implicate polystyrene MPs as a cause of alterations in the sex ratio and weight of offspring in mice, as well as a dysfunction of the lipid and amino acid metabolisms; therefore, there is the potential for interfering with the physiological functions of future generations [44]. Microplastics and nanoplastics induce an imbalance in reproductive hormone concentrations, in particular T4, FSH, LH and AMH.

In addition, to plastic particles, three plastic additives (Bisphenol A, phthalates and polychlorinated biphenyl 153) have been identified as causing infertility. These are defined as endocrine-disrupting chemicals (EDCs), as they are able to interfere with the endocrine system, thus mimicking hormonal active agents.

Bisphenol A(BPA) it is a xenoestrogen with estrogen-mimicking, hormone-like properties. It can bind to estrogen (ERs) and androgen (AR) receptors, thus interfering with steroidogenesis in Leydig cells, including 17α-hydroxylase/17,20 lyase and aromatase functions, interfering with LH receptor-ligand binding [47]. DEHP interacts with estrogen metabolism by suppressing the enzyme aromatase, which is necessary for the conversion of testosterone to estradiol and has an important role in brain sexual differentiation [48]. Ding et al. [49] described the negative effects of BPA on female mouse fertility, which were due to impaired cytoskeletal dynamics in the oocyte, induction of oxidative stress, increased DNA damage and epigenetic alterations in oocytes. The BPA compounds can affect the follicular, ovarian and the hypothalamic systems, granulosa and theca cells and induce the formation of progressive proliferative lesions on the oviduct and

uterus, such as atypical hyperplasia, stromal polyps and endometriosis. Lambs exposed to BPA had reduced follicular ovarian reserves with a lesser population of primordial follicles, an increase in antral atretic follicles, a greater prevalence of follicles containing multiple oocytes and reduced ovarian weights [47]. Fujimoto et al. [50] observed an association between a greater concentration of BPA in the serum of women and decreased likelihood of mature oocytes. Saleh et al. [51] also reported that BPA increased apoptotic gene expression in bovine oocytes. Relatively greater concentrations of BPA were detected in the urine of infertile compared with fertile women and in those with polycystic ovary syndrome (PCOS), where an association between the BPA content and greater androgen concentrations were observed [52]. BPA has also been detected at different concentrations in the serum of pregnant and nonpregnant women, follicular fluid, fetal serum and amniotic fluid [53]. There was no BPA detected in the follicular fluid of pigs, but BPA alters the hyaluronic acid production and gene expression of cumulus cells and disrupts the spindle formation and meiosis in oocytes [54].

Concerning the hypothalamic–pituitary–gonadal axis (HPGA), BPA interferes with a gonadotropin synthesis by reducing the relative abundance of gonadotropin mRNA, GnRHr, and Nr5al [55]. Additionally, the detection of BPA was associated with a reduced cleavage rate and development of embryos at the blastocyst stage and alteration in gene expression in cattle [56]. From results of several studies there is a positive correlation between maternal BPA and both weight/size of the offspring [57][58]. Other studies, such as Talpade et al. [59], have led to results indicating adverse effects of BPA in chickens (*Gallus domesticus*), such as increased embryo mortality and the malformation of reproductive organs.

On the other hand, in 98% of men with infertility problems, there is a correlation between urinary BPA and sperm count and motility [60]. BPA alters the energy metabolism and reduces sperm storage, sperm transit time and mitochondrial activity while increasing the apoptosis of Sertoli cells, the percentage of immature sperm and sperm DNA damage, thus determining the lesser semen quality [47][61][62]. These alterations have also been found in dogs, cats and goats, while the possibility of an increased prevalence of prostate cancer has been suggested [56]. In some studies, there have been associations of BPA with sexual functions, erectile functions, ejaculation, cryptorchidism and congenital genital malformations in males [47]. In some comparative studies, it was concluded that BPA causes abnormalities in meiosis, spindle fibers and congenital defects in mice, pigs, cattle and humans [56][63].

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