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The adverse health effects of increasing microplastic pollution on aquatic mammals

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ABSTRACT

Microplastics (MPs), an emerging ubiquitous pollutant in the aquatic ecosystem, pose serious health concerns to the survival of aquatic fauna, especially top predators (e.g., aquatic mammals). It is challenging to investigate the toxicological profile of MPs in aquatic mammals due to their diverse toxicological behaviour, physico-chemical properties, and other technical and ethical issues. This study reviewed the current burden of MPs in the aquatic ecosystem, the occurrence of MPs in the various tissues of aquatic mammals, its composition (heavy metals, pesticides, pathogens), and possible health effects on individual and population levels in aquatic mammals. Aquatic mammals are constantly exposed to MPs directly and indirectly via the food-web. The MPs and a wide range of toxic heavy metals, pesticides, and pathogens added during manufacturing or adsorbed from the surrounding environments are bioaccumulated in aquatic mammals for years. Due to their long life-span and heavy body masses, these pollutants can cause several serious health issues in aquatic mammals that can drastically reduce the population size and ultimately can cause extinction, especially in vulnerable populations. Still today the toxicological profile of MPs and its presence in other deep tissues largely remains unknown in aquatic mammals. We therefore suggest a global assessment of the risks associated with the consumption of MPs by aquatic mammals and the presence of MPs in their habitats.

1. Introduction

Aquatic mammals are the charismatic megafauna and prime sentinel species due to their long-life spans, apex position in the trophic web, long-term coastal residents, and remarkable fat reserves that serve as depots for anthropogenic toxins (Moore, 2008; Bossart, 2011). These mammals have an essential role in influencing the structure and function of the marine environment (Moore, 2008). Currently, many aquatic mammals are of conservation concern due to escalating anthropogenic activities, including plastic and other chemical pollution (Avila et al., 2018; De Sá et al., 2018; Nabi et al., 2018a; Nabi et al., 2018b; Meaza et al., 2021; Nabi et al., 2021). However, there is limited knowledge of the many anthropogenic contaminants in aquatic ecosystems regarding the relationship between the widespread microplastics (MPs) and the well-being of aquatic mammals. The key objective of this study is to provide an overview of the MPs bioaccumulation and their possible health consequences in aquatic mammals.

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2. Rising plastic pollution in aquatic ecosystem

Plastic waste is a modern societal and ecological issue due to its convenience and ubiquitous use in daily life and associated long-term harmful effects on the ecosystems and organisms after careless disposal (Galloway et al., 2017). Plastic constitutes approximately 60–80% of the debris in a marine environment and is currently considered as a significant threat to marine biodiversity above all other environmental hazards, including different types of pollution, climate change, resource overexploitation, and invasive species (Derraik, 2002; Halpern et al., 2008; Nabi et al., 2018a; Nabi et al., 2018b). They are transported far and wide by winds, rivers, and ocean currents. Every year, approximately 5–13 million tonnes of plastic debris end up in the ocean ranging from the coastline, seafloor, mid-ocean gyres, and ultimately, in remote polar regions (Jambeck et al., 2015; Van Sebille et al., 2015; Peeken et al., 2018; Mendes et al., 2021; Osorio et al., 2021). Currently, an estimated 24.4 trillion plastic pieces ($\sim$57.8 $\times$ 10^4 tonnes) are found in the world's upper ocean (Isobe et al., 2021), and by the year 2025, the weight of plastic debris in the marine environment could increase to 250 million metric tonnes (Jambeck et al., 2015). Furthermore, during the ongoing COVID-19 pandemic, a large quantity of plastic waste has been generated globally. According to Peng et al. (2021), over eight million tons of plastic wastes have been generated globally amidst the COVID-19 pandemic, with over 25,000 tons entering the ocean. In total, 11 million tons of mismanaged plastic waste will be generated by the COVID-19 pandemic; among them, 34,000 tons of plastic waste will enter the ocean (Peng et al., 2021). Sun et al. (2021) reported that approximately 1370 trillion MPs would enter the global coastal marine environments by 2020 from surgical masks discarded throughout the world. Plastic waste is resistant to oxidative damage, heat, and degradation due to its physical and chemical nature. It persists for a long time in the marine ecosystem and is therefore characterized as an environmental contaminant (Andrady, 2011; Vroom et al., 2017).

3. Microplastics in aquatic ecosystem

MPs (<5 mm) are persistent synthetic particles ubiquitously found in a wide range of aquatic ecosystems (Bravo Rebolledo et al., 2013; Vroom et al., 2017). Depending on their shape, density, and composition, MP can sink, be neutrally buoyant, and float (Hernandez-Gonzalez et al., 2018). The density of MPs in the ocean surface water ranged from 5 to 70 particles per m-^{2} (Ter Halle et al., 2017), whereas in coastal water, it is six items m-^{3} (Cole et al., 2011). In rivers surface water, the density of MPs is very high, ranging from 1,580 to 57,665 particles/m^3 (Osorio et al., 2021). The marine environment is a major sink for MPs (plastic soup) where they are found in two different ways either primary MPs such as microspheres or MPs pellets and secondary MPs resulting from the degradation of larger fragments (Fig. 1; Andrady, 2017; Ross et al., 2021). MPs originate from various sources, including macro-plastics degradation (by UV light, physical abrasion, wave action), shipping spills, and wastewater discharge from industries and other sources containing microbeads and microfibers (Nelms et al., 2018; Du et al., 2021). Currently, research interest is developing to investigate the consequences of MPs on the aquatic eco-health and the organism within it. Due to their small size, MPs are ingested by a variety of taxa, including aquatic mammals either accidentally (indiscriminate feeding strategies users, e.g., filter feeders), misidentification of MPs for prey, via inhalation, and indirectly due to the trophic transfer (raptorial feeding strategy users, e.g., dolphins) by consuming contaminated prey (Hocking et al., 2017; Nelms et al., 2018; Meaza et al., 2021). Despite direct ingestion of MPs, macro-plastics ingested are fragmented into smaller pieces within the gastro-intestinal tract (GIT) of aquatic mammals (Nelms et al., 2018; Huang et al., 2021). According to Lusher et al. (2016), 11% of mesopelagic fish in the Irish waters contained MPs and approximately, 463 million MPs could be ingested by a single striped dolphin annually.

4. Mps in aquatic mammals

To date, approximately 3876 species have been reported to be affected by marine debris (https://litterbase.awi.de/interaction_detail; date accessed, April 4, 2022). Among them, being an apex predator, plastic debris ingestion has been reported in 123 aquatic mammalian species, including 36 % of seals (12 of 33), 59 % of whales (47 of 80), and overall, 63% of all cetacean species (Bergmann et al., 2015; Fossi et al., 2018). However, due to logistic, technical, and ethical issues, few studies have recently reported the presence of MPs in the GIT (Bravo Rebolledo et al., 2013; Besseling et al., 2015; Lusher et al., 2015; Lusher et al., 2018; Hernandez-Gonzalez et al., 2018; Van Franeker et al., 2018; Xiong et al., 2018; Nelms et al., 2019; Zhu et al., 2019; Moore et al., 2020; Haave et al., 2021) and fecal samples ((Eriksson and Burton, 2003; Perez-Venegas et al., 2018; Nelms et al., 2018; Donohue et al., 2019; Hudak and Sette, 2019; Perez-Venegas et al., 2020) in more than 21 species of aquatic mammals across the globe (Table 1). The total number of MPs/individuals in these aquatic mammals ranges up to 411 in the stomach (Hernandez-Gonzalez et al., 2018) and 584 in the scats (Donohue et al., 2019). Furthermore, the presence of MPs in the grey seals living in a sanctuary (Nelms et al., 2018), where anthropogenic pollution is low, suggests the omnipresence of MPs even in environmentally controlled areas. The size range of MPs reported in aquatic mammal's scats and GIT content are highly heterogeneous and range from 0.1 to 5 mm (Meaza et al., 2021). Fibers shape MPs are the most abundant MPs in the GIT (Hernandez-Gonzalez et al., 2018; Xiong et al., 2018; Zhu et al., 2019; Nelms et al., 2019), while fragment shape MPs are ubiquitous in the scats of aquatic mammals (Eriksson and Burton, 2003; Hudak and Sette, 2019; Donohue et al., 2019; Perez-Venegas et al., 2020). Different colours of MPs, including green, white, black, and blue, are reported in the GIT and scats (Xiong et al., 2018; Lusher et al., 2018; Hernandez-Gonzalez et al., 2018; Perez-Venegas et al., 2020), while scats often additionally contained yellow, brown, purple, and red colour MPs (Meaza et al., 2021). The most common polymer types reported are polyether-sulfone, nylon, cotton, polyester, polyethylene, polypropylene, and ethylene-propylene (Nelms et al., 2019; Meaza et al., 2021). However, others include cellophane, alkyd resin, low-density polyethylene, polyamide resin, acrylic, polyvinyl chloride, polystyrene, cellulose, polycarbonate, and polyolefin, have also been reported in aquatic mammals (Meaza et al., 2021). The current knowledge linked to thFe toxicities of MPs in aquatic mammals is scanty; however, the lack of studies should not be interpreted as evidence of no risk. MPs toxicities could be detrimental, especially to endangered and critically endangered species populations dwelling in highly polluted areas. Furthermore, considering the escalating rise of plastic debris in water bodies, the morbidities and mortalities in aquatic mammals due to MPs will become more evident if comprehensive studies are carried out using advanced sensitive techniques.

5. Why MPs are dangerous for aquatic mammals

Several hundreds of chemicals are either added or adsorbs by the MPs, including phthalates, organochlorine contaminants (HCB, DDTs, PCBs), persistent organic pollutants, organophospho-

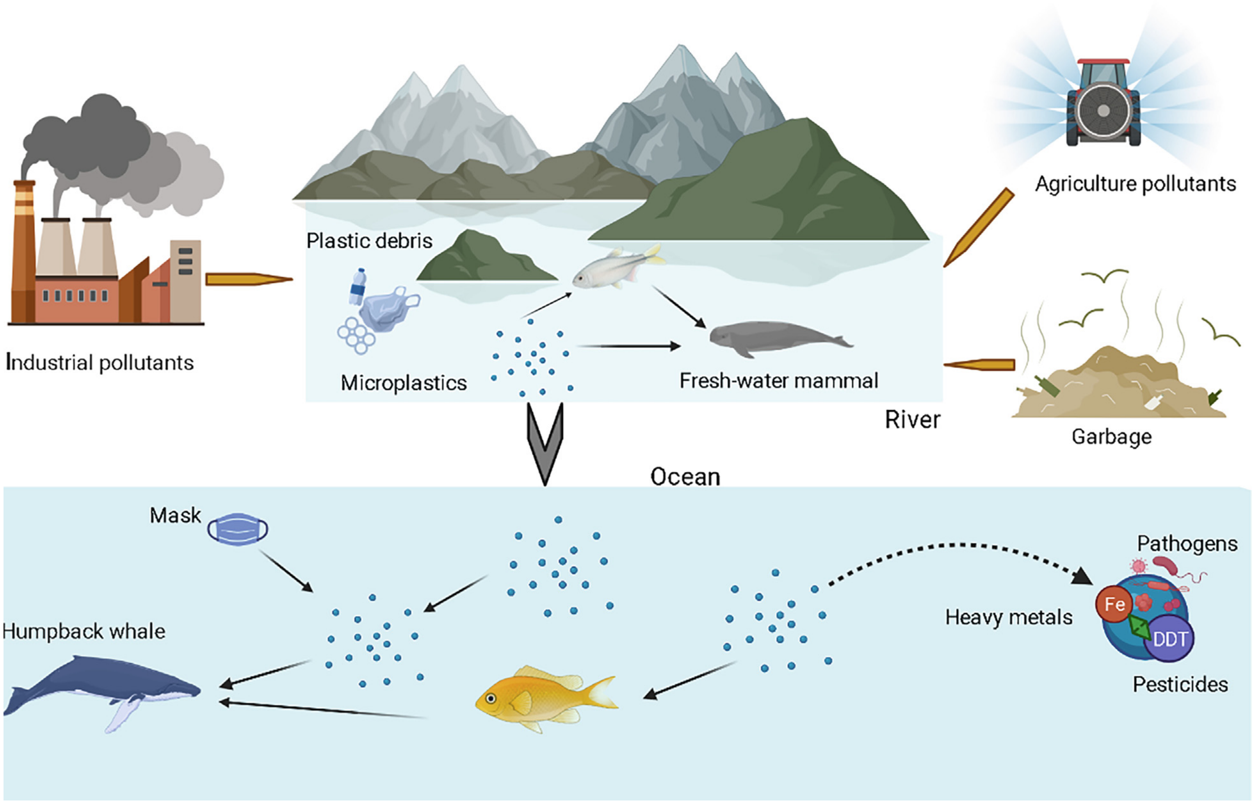

Fig. 1. The primary and secondary microplastics loaded with pathogens and a wide range of chemical pollutants from various sources entered the aquatic ecosystem. The aquatic mammals ingest the microplastics directly from the environment and via the food-web. (Biorender.com)

rus esters, dioxins, antibiotics, tributyltin, bisphenol A, aluminium oxide, chromium, lead, cadmium, antimony, and other chemical ingredients (Ylitalo et al., 2005; Fossi et al., 2014; Fossi et al., 2016; Kedzierski et al., 2018; Campanale et al., 2020; Barrick et al., 2021; Meaza et al., 2021). Due to the contaminant's hydrophobicity, these contaminants have a greater affinity for MPs than natural sediments and seawater. Therefore, MPs act as a vector of pollutants and toxins, which, along with the biomagnification and bioaccumulation process, makes MPs a potential threat to the well-being of aquatic mammals (De Sá et al., 2018). MPs ingestion can cause a reduction in energy reserves, feeding capacity and reproductive outputs, detrimental alterations in the GIT physiology, depressed immune system, vulnerability to diseases, oxidative stress, cytotoxicity, and differential expression of genes, mainly studied in lower trophic animals (Hall et al., 2006; Kedzierski et al., 2018; Nabi et al., 2019; Amin et al., 2020; Meaza et al., 2021; Ugwu et al., 2021). MPs ingestion can alter the kidney histomorphology, induce inflammation, and disrupt several biomarkers (Meng et al., 2022). Furthermore, MPs exposure can cause oxidative and epithelial damage in the gut, immune cell toxicity, microbial disorder, and reduction of the mucous layer.

6. Pollutants in MPs and its biomagnification and effects on aquatic mammals

The MP's larger surface area-to-volume ratio and hydrophobic surface make them a suitable sorbent for many toxic chemicals, including heavy metals and organic chemicals (Verla et al., 2019; Wang et al., 2020). The loaded MPs, therefore, act as a conveyor ("Carrier effects") of toxic pollutants (Verla et al., 2019; Wang et al., 2020) and increase the bioaccumulation of sorbed pollutants in aquatic mammals directly and indirectly via the food web. Unlike seawater, gut surfactants accelerate the release of hydrophobic organic pollutants ("releaser effects") from MPs and bioaccumulate them in the different tissues (Lee et al., 2019). In aquatic mammals, MPs are only reported in the GIT and scats (Table 1); however, a large number of metals and organic pollutants bioaccumulated in the different tissues (Lungs, liver, kidneys, skin, muscle, blubber, bone, testes, ovaries, blood) of many aquatic mammalian species have been reported across the world (Table 2). On the one side, pollutants bioaccumulation in different tissues depends on the nature of MPs. However, on the other hand, MPs/nano-plastics in aquatic mammals, like other organisms, may cross the cell membrane and blood–brain barrier, enter into the blood circulation and bioaccumulate in the other vital internal organs (brain, liver, kidney, placenta) along with other pollutants (Prietl et al., 2014; Shelver and Banerjee, 2021). Further studies are needed to confirm the presence of MPs in these deep tissues of aquatic mammals. In addition, further studies in aquatic mammals need to investigate MPs in the internal tissues and their correlation with other pollutants. Furthermore, the transplacental transfer of heavy metals, pesticides, and other pollutants to the fetuses of aquatic mammals (Teigen et al., 1999; Alonso et al., 2015; Zanuttini et al., 2019) and MPs to the fetuses of other species in mammals (Fournier et al., 2020; Ragusa et al., 2021) also provides a hint that MPs could bioaccumulate in aquatic mammals during fetal development. Accumulation of heavy metals and organic pollutants causes several ill effects, including congenital disabilities, endocrine disruption, immune system dysfunction, vascular damage, nervous system disorders, kidney and gastrointestinal dysfunction, and cancer (Nabi et al., 2017a,b; Nabi et al., 2020a; Balali-Mood et al., 2021). Pesticides can cause an increase in oxidative stress, producing superoxide, and alter different liver func-

Table 1
Microplastics reported in different species of aquatic mammals globally.

Species	Location	Sample	References
White-beaked dolphin Striped dolphin Risso's dolphin Pygmy sperm whale Harbour seal Harbour porpoise Grey seal Short-beaked common dolphin Bottlenose dolphin Atlantic white-sided dolphin	British coast	GIT	Nelms et al., 2019
True's beaked whale Cuvier's beaked whale Common dolphin Striped dolphin Harbour porpoise Killer whale Bottlenose dolphin	Ireland	GIT	Lusher et al., 2015 Lusher et al., 2018
Humpback whale	Netherland	Intestine	Besseling et al., 2015
Harbour porpoise		Stomach	Van Franeker et al., 2018
Harbour seal		GIT	Bravo Rebolledo et al., 2013
East Asian finless porpoises	China		Xiong et al., 2018
Indo-Pacific humpback dolphins		Intestine	Zhu et al., 2019
Common dolphin	Iberian Peninsula	Stomach	Hernandez-Gonzalez et al., 2018
Beluga whale	Canada	GIT	Moore et al., 2020
Otters	Norway	Stomach	Haave et al., 2021
Northern fur seals	USA	Scats	Donohue et al., 2019
Harbour seal, gray seal			Hudak and Sette, 2019
Fur seals	Macquarie Island Guafo Island	Scats	Eriksson and Burton, 2003 Perez-Venegas et al., 2018
Otariids	Peru and Chile	Scats	Perez-Venegas et al., 2020
Grey seals	UK	Scats	Nelms et al., 2018

tions, including detoxification, metabolism, and immunity, resulting in an increase in ROS in the liver (Chen et al., 2021). In response to liver toxicity, hepatocyte inflammation, degeneration, mitochondrial dysfunction, and apoptosis occur (Karami-Mohajeri et al., 2017).

The combination of heavy metals to heavy metals, heavy metals to pesticides, and pesticides with pesticides act synergistically and exhibits higher toxicity than a single molecule alone. When combined, the toxic hazards of a single component can be modified, resulting in unexpected adverse health consequences. The combined interactions of these xenobiotics (heavy metals, pesticides, etc.) in MPs could produce synergistically significant adverse effects on neurotoxicity, cytotoxicity, immunotoxicity, infertility, and several metabolic functions (Singh et al., 2017). Given aquatic mammals' long life-span and their exposure to a mixture of xenobiotics, the synergistic interactions among xenobiotics in aquatic environments could have several negative effects on health, and further research is needed to address these issues. Unfortunately, aquatic mammals have convergently lost the traits, including *Paraoxonase 1*, which encodes a bloodstream enzyme that hydrolyzes organophosphate compounds (Meyer et al., 2018). The loss of this enzyme and the escalating rise of organophosphate compounds in MPs pose severe risks to vulnerable populations in the modern environment.

7. EDCs in MPs and aquatic mammals

Over 1000 chemicals reported as endocrine disruptor chemicals (EDCs) are found globally in different ecosystems (Kassotis and Trasande, 2021). EDCs comprise the MPs themselves (Amereh et al., 2020) and a diverse group of fungicides, pesticides, metals, phytoestrogens, pharmaceutical agents, nonylphenols, plasticizers, industrial chemicals etc., (Yilmaz et al., 2020; Ullah et al., 2021a; Ullah et al., 2021b) are transported by MPs to remote areas including the Arctic (Barrick et al., 2021; Meaza et al., 2021; Routti et al., 2021) and bioaccumulate in aquatic mammals (Routti et al., 2021; Table 2). Most EDCs are lipophilic; they bioaccumulate in adipose tissues, are resistant to metabolism, slowly excreted, and, therefore, have a long half-life in the body (Rodprasert et al., 2021). These EDCs can bind to the body's endocrine receptors, leading to activation, blocking, or alteration of natural hormone synthesis and degradation through various mechanisms, resulting in abnormal, lack, or false hormonal signals that can increase or inhibit normal endocrine function (Yilmaz et al., 2020; Rodprasert et al., 2021). Aquatic mammals are sensitive to the toxicological effects of EDCs (Fossi and Marsili, 2003). Several studies have reported the effects of diverse group of EDCs and their effects on aquatic mammals (Table 3). However, the impacts of EDCs are challenging to assess because their adverse effects develop latently and manifest at a later age (Kassotis and Trasande, 2021). EDCs affect the reproductive system and survival through endocrine disruption and immune suppression, which have population-level effects in a region (Sonne et al., 2010). In addition, the EDCs can impair development, reproduction, thyroid functions and metabolism, cause cancer, neurological issues, and gestational disorders including, fetal growth restriction, miscarriage, and preterm birth (Desforges et al., 2018; Murphy et al., 2018; He et al., 2021; Schjenken et al., 2021; He et al., 2021).

EDCs, when used in combination, result in outcomes that cannot be predicted from their individual behavior (Delfosse et al., 2021). For example, a mixture of phthalates such as DEHP + DBP (Tian and Li, 2010), polyfluoroalkyl substances (Preston et al., 2020), and fenvalerate and thiophanate-methyl (Wang et al., 2021), significantly disrupt the thyroid glands normal function relative to the individual chemical exposure. Several EDCs chemicals produce estrogen-like effects (Guo et al., 2021) and 66 of 200 pesticides tested reported antiandrogenic activity (Kojima et al.,

Table 2
Pollutants linked with microplastics reported in aquatic mammals.

Species	Tissues	Pollutants	References
Bottlenose dolphin Common dolphin Striped dolphin Risso's dolphin Atlantic spotted dolphin white-beaked dolphin Spinner dolphin Rough-toothed dolphin Indo-pacific humpback dolphin Irrawaddy dolphins Hector's dolphin Gervais' beaked whale Pygmy sperm whale Pygmy killer whale Dwarf sperm whale melon-headed whale Cuvier's beaked whale Humpback whale Killer whale False killer whale Beluga whale Bowhead whale Fin whale, mink whale Pilot whale Dall's porpoise Harbour porpoise Yangtze finless porpoise Northern fur seals Southern Sea lion Ringed seal Harbor seal Walrus Polar bear Manatees Dugong	Lung, liver, kidney, skin, muscle, blubber bone, testes, ovaries, blood	Cadmium, Cobalt, Iron, Manganese, Magnesium, Sliver, Nickle, Selenium, Zinc, Copper, Lead, Thallium, Mercury, Arsenic, Chromium, Strontium, Tin, Vanadium, Aluminium, Titanium, Uranium, Antimony, Beryllium, Gold, Barium, Lithium, Molybdenum, Platinum Aldrin, Dieldrin, DDT, DDD, DDE, PCB, Chlordane, Toxaphene, Heptachlor epoxides, Bisphenol A, Atrazine, Diethyl phthalate, Nonylphenol ethoxylate, Triclosan, Perfluoroalkyl phosphinic acids, Organochlorine, Dicofol, Polychlorinated biphenyls, Polybrominated diphenyl ethers, Endosulfan, Dioxin related compounds, Pyrethroid pesticides, Ultra-violet filters	Becker, (2000) Nielsen et al., (2000) Frodello and Marchand, (2001) Ikemoto et al., (2004) Haynes et al., (2005)Kannan et al., (2005) Das et al., 2006 Gerpe et al., 2007 McHugh et al., (2007) Fair et al., (2010) Niño-Torres et al., (2010) Stockin et al., (2010) Aubail et al., (2013) Siegal-Willott et al., (2013) Alonso et al., (2015) De Silva et al., 2016 Hansen et al., (2016) Takeuchi et al., (2016) Mackintosh et al., (2016) Gui et al., (2017) Aznar-Alemany et al., (2017) Wise et al., 2019 Xiong et al., (2019) Zanuttini et al., (2019) Page-Karjian et al., (2020)

2004). The combined mixture of cypermethrin and malathion (Guo et al., 2021) and a mixture of phthalate ester (Gao et al., 2017) synergistically increase the estrogenic effects and disrupt the endocrine signaling system.

When EDCs interact with the thyroid hormone axis and estrogen receptors, they form reactive oxygen species (ROS) and increase oxidative stress, resulting in impaired reproductive growth (Park et al., 2020). The Hypothalamic-pituitary-adrenal (HPA) axis, which controls the stress system, immune system, emotions, and reproduction, may be involved in these interactions (Salgado-Freiría et al., 2018); however, there are a limited number of EDCs mixture studies related to HPA axis effects. Based on limited studies, exposure to various EDCs mixtures considerably increases ROS production, stress response genes, immune-related genes, and oxidative stress enzymes in vertebrates (Hamid et al., 2021). Furthermore, there is limited literature about the deleterious epigenetic multi- and transgenerational effects of EDCs mixture. In a few studies, rats developmentally exposed to a mixture of EDCs showed multi- and transgenerational effects, including a significant increase in kidney diseases, reproductive and metabolic disorders, and behavioural alterations (López-Rodríguez et al., 2021).

Considering the significant effects of EDC on wildlife health and existence, it is essential to identify MPs dense regions and pay serious attention to the aquatic wildlife within, especially threatened populations. It is also important to know how many EDC are in the MPs? Where do they come from, and what is their mechanism of action? When used individually or in combination, what are their deleterious effects during development, adulthood, and across generations?

8. MP-linked chemical pollutants and cancer in aquatic mammals

Even at low concentrations, chronic exposure to heavy metals promotes chronic inflammation and subsequently develops carcinogenesis (Balali-Mood et al., 2021). Among the principal metals, including lead, aluminum, silver, arsenic, beryllium, copper, chromium, mercury, cadmium, nickel, radium, and cobalt reported in aquatic mammals (Table 2), can cause lung, brain, skin, liver, gastrointestinal tract, larynx, urinary bladder, kidney, prostate cancer, and leukemia (Cruz et al., 2021; Gallicchio and Harper, 2021). Similarly, several heavy metals, pesticides, and biocides bioaccumulated in aquatic mammals can cause cancer in the endocrine

Table 3
Endocrine disruptors and their effects on aquatic mammals.

Species	Endocrine disruptors	Targeted endocrine glands/effects	References
Blue whales	Phthalates		He et al., 2021
Fin whales	POPs		Kimberley et al., 2021
Grey seals	PBDE		Routti et al., 2019
Male walruses	PCBs	Thyroid glands	Villanger et al., 2011
Beluga whales	POC		Hall et al., 2003
Northern elephant seals			Beckmen et al., 1997
Killer whale			Desforges et al., 2018
Harbor porpoises			Murphy et al., 2018
Common dolphin	PCBs	Reproductive failure	Murphy et al., 2015
Habor seal	Organochlorines		Reijnders,1999
Gray and Ringed seal			
Beluga whale			
Grey-seals, Ringed seals	POP	Sex hormones	Troisi et al., 2020
	PCB		
Bottlenose dolphin	HOC	Testosterone	Trego et al., 2019
Short-beaked common dolphins		Testosterone	Trego et al., 2018
Harbor seals	PCBs	Testosterone, progesterone	Troisi and Mason, 2000
Bottlenose dolphins	DDT	Androgen, cortisol	Galligan et al., 2019
			Ropstad et al., 2006
		Thyroid glands	Braathen et al., 2004
Polar bears	PCBs	Progesterone	Oskam et al., 2004
	Organochlorines	Testosterone	Haave et al., 2003
		Cortisol	Oskam et al., 2003
			Skaare et al., 2001
Beluga whale	PAH	Gonadal cancers	
Pilot whale			Murphy et al., 2018
Blue whale			Martineau et al., 2002
Fin whale			
Harbor porpoise			
Bottlenose dolphin			
Other cetaceans			

PCBs, Polychlorinated Biphenyls; POPs, Persistent Organic Pollutants; POC, Persistent Organohalogen Compound; PBDE, Polybrominated Diphenyl Ethers; HOC, Halogenated Organic Compounds; PAH, Polycyclic Aromatic Hydrocarbons.

glands, including the thyroid, testes, ovary, prostate, and mammary glands (Lauretta et al., 2019). In addition, heavy metals disrupt many cellular functions, such as growth, proliferation, differentiation, damage DNA repair systems, apoptosis, and genomic stability (Balali-Mood et al., 2021). A review of the mechanisms of action reveals that these metals exert similar toxic effects: they produce ROS, enzyme inactivation, weaken antioxidant defenses, oxidative stress, and ultimately lead to carcinogenesis (Balali-Mood et al., 2021).

Currently, 168 pesticides are classified as potential carcinogens (Schwingl et al., 2021). Several carcinogenic pesticides have the potential to cause genitourinary, gastrointestinal, central nervous system, pulmonary system, renal, and endocrine glands cancer (Varghese et al., 2020; Cazzolla Gatti, 2021; Schwingl et al., 2021) are bioaccumulated in aquatic mammals (Table 2). Pesticide-mediated carcinogenesis may involve several mechanisms, including inflammation, oxidative stress, immunotoxicity, endocrine disruption, and genotoxicity (Gangemi et al., 2016). Although cetaceans are more anticancer resistant relative to other mammals (Tejada-Martinez et al., 2021), however, studies have reported neoplastic incidents in 40 species of aquatic mammals (Kitsoulis et al., 2020) and suggested cancer as one of the significant causes of death in aquatic mammals (Martineau et al., 2002; Gulland et al., 2020). For example, beluga whales exposed to a high concentration of polycyclic aromatic hydrocarbons in Canada have a percentage of cancer similar to humans (Martineau et al., 2002). Similarly, in California sea lions, the prevalence of urinogenital cancer linked with organic chemical pollutants is one of the highest amongst mammals (Gulland et al., 2020). To our knowledge, till date, no studies are available linking MPs directly with cancer in aquatic mammals despite the rising concentration of MPs and the increasing incidence of cancer in aquatic mammals. Although it is challenging to study cancer in aquatic mammals due to their inaccessibility, lack of exposure history to MPs and co-contaminants, and logistical, ethical and legal constraints on experimentation. However, understanding the link between cancer and MPs and its co-contaminant in aquatic mammals will not only help in biodiversity conservation, but due to their long lifespans, large body masses, and long-term exposure to MPs and associated chemical contaminants, aquatic mammals may represent an ideal animal model to understand the mechanism of carcinogenesis.

9. MPs-linked pathogens and risk of infectious diseases in aquatic mammals

MPs in the aquatic environments provide a novel microhabitat and protective ecological niche (plastisphere) with high selectivity and plasticity to a variety of distinct communities of pathogens, including antimicrobial-resistant pathogens (Amaral-Zettler et al., 2020; Bowley et al., 2021; Gkoutselis et al., 2021; Pham et al., 2021). These novel pathogens on MPs are dispersed over long distances by waves, currents, and winds to alien communities, transmitted to potential hosts, and can cause disease outbreaks (Bowley et al., 2021). The plastisphere acts as hotspots of antimicrobial resistance and houses 100–5000 times more antimicrobial resistance bacteria than the surrounding water (Yang et al., 2019; Zhang et al., 2020). Furthermore, the plastisphere communities enhance the metabolic pathways that contribute to infectious diseases (Sun et al., 2020). Therefore, the MPs not only act as a hub and a carrier for microbial pathogens but also enrich pathogenic strains through pathogenicity islands and antimicrobial properties during horizontal gene transfer (Bowley et al., 2021). One study reported direct pathogen transfer via plastic (Rotjan et al., 2019). Many studies have postulated pathogen transfer via plastic in several organisms (Viršek et al., 2017; Lamb et al., 2018; Frère et al., 2018; Amaral-Zettler et al., 2020). However, there are no studies if pathogen-colonized MPs can transfer pathogens and cause disease in aquatic mammals even though aquatic mammals ingest a considerable quantity of MPs directly and indirectly via the food-web as an apex predator. From a conservation and wildlife management point of view, it is a vital area of research to understand the role of MPs as a pathogen vector, especially in the vulnerable populations of aquatic mammals native to the MPs dense regions.

Microorganisms on the plastisphere can use the added or adsorbed metals (e.g., iron, cobalt, copper, zinc, manganese) as micronutrients (Begg, 2019; Amaral-Zettler et al., 2020). These metals are also essential for the ultimate survival and virulence of many pathogenic microorganisms (Begg, 2019). MPs and loaded pollutants can cause pulmonary cytotoxicity, disrupt the protective pulmonary barriers (Dong et al., 2020; Facciolà et al., 2021), and allow the entry of opportunistic and newly introduced pathogens to the deep parts of the lungs leading to respiratory infections and other infectious diseases in aquatic mammals (Nabi et al., 2020b; Bowley et al., 2021). Furthermore, metals such as mercury and cadmium have immunosuppressive effects and are liked with a higher rate of infectious diseases in aquatic mammals (Bennett et al., 2001; Pellissó et al., 2008). Currently, Labrado (2019) reported a positive correlation between a higher number of diseased animals and MPs per square kilometer in aquatic mammals. Similarly, Nelms et al. (2019) found that aquatic mammals that died due to infectious disease had a higher number of MPs relative to other drivers of mortality. Both viruses and bacteria that can cause infectious diseases, especially pneumonia, are the leading cause of death in aquatic mammals (Nabi et al., 2020b). During different infectious pneumonia outbreaks in the past, the mortality of thousands of individuals in different aquatic mammal species has been reported across the globe (Nabi et al., 2020b). All the evidence indicates that MPs in aquatic mammals can act as a vector for pathogen transmission. However, studies are required to understand the extent to which MPs can act as a vector for pathogens and toxicants from the aquatic environment into the tissues and their pathogenicity and virulence potential in aquatic mammals.

10. Conclusion

This review represents a warning signal of the rising level of MPs and their associated toxicants and pathogens in the aquatic environment and its potentially hazardous effects on aquatic top predator mammals. It suggests an urgent need for continuous monitoring to avoid reductions in population and biodiversity in both fresh-water and marine environments. Further studies are needed to deeply investigate the MPs burden globally in the aquatic environment, their accumulation in the different tissues of aquatic mammals, and possible physiological dysfunctions.

CRediT authorship contribution statement

Ghulam Nabi: Writing – original draft. **Shahid Ahmad:** Writing – review & editing. **Sana Ullah:** Writing – review & editing. **Sahib Zada:** Writing – review & editing. **Maliha Sarfraz:** Writing – review & editing. **Xinle Guo:** Funding acquisition. **Muhammad Ismail:** Writing – review & editing. **Kunyuan Wanghe:** Funding acquisition.

Declaration of Competing Interest

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

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