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## Review article



## Linking pollution and cancer in aquatic environments: A review

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## ABSTRACT

Due to the interconnectedness of aquatic ecosystems through the highly effective marine and atmospheric transport routes, all aquatic ecosystems are potentially vulnerable to pollution. Whilst links between pollution and increased mortality of wild animals have now been firmly established, the next steps should be to focus on specific physiological pathways and pathologies that link pollution to wildlife health deterioration. One of the pollution-induced pathologies that should be at the centre of attention in ecological and evolutionary research is cancer, as anthropogenic contamination has resulted in a rapid increase of oncogenic substances in natural habitats. Whilst wildlife cancer research is an emerging research topic, systematic reviews of the many case studies published over the recent decades are scarce. This research direction would (1) provide a better understanding of the physiological mechanisms connecting anthropogenic pollution to oncogenic processes in non-model organisms (reducing the current bias towards human and lab-animal studies in cancer research), and (2) allow us to better predict the vulnerability of different wild populations to oncogenic contamination. This article combines the information available within the scientific literature about cancer occurrences in aquatic and semi-aquatic species. For the first aim, we use available knowledge from aquatic species to suggest physiological mechanisms that link pollution and cancer, including main metabolic detoxification pathways, oxidative damage effects, infections, and changes to the microbiome. For the second aim, we determine which types of aquatic animals are more vulnerable to pollution-induced cancer, which types of pollution are mainly associated with cancer in aquatic ecosystems, and which types of cancer pollution causes. We also discuss the role of migration in exposing aquatic and semi-aquatic animals to different oncogenic pollutants. Finally, we suggest novel research avenues, including experimental approaches, analysis of the effects of pollutant cocktails and long-term chronic exposure to lower levels of pollutants, and the use of already published databases of gene expression levels in animals from differently polluted habitats.

## 1. Introduction

Pollution, together with climate change and over-exploitation, is one of the most severe consequences of the anthropocene for both marine and freshwater ecosystems (Häder et al., 2020). Toxic substances such as persistent organic pollutants, pesticides, and heavy metals, but also pharmaceuticals and microplastics, have been shown to negatively

affect the health and survival of aquatic organisms (Carolin et al., 2017; Duis & Coors, 2016; Morrissey et al., 2015; Li, 2014; Zhou et al., 2010). Due to the interconnectedness of aquatic ecosystems through the highly effective marine and atmospheric transport routes, all aquatic ecosystems are potentially vulnerable to pollution (Häder et al., 2020), and therefore, the effects of pollution on the health of aquatic organisms requires urgent attention from the scientific community.

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As the negative impact of anthropogenic pollution on aquatic and semiaquatic organisms has been widely acknowledged, the next step should be to focus on specific physiological pathways and pathologies linking pollution to wildlife mortality. Whilst the release of large quantities of pollutants can cause an acute impact, measured by large-scale sudden mortalities of aquatic organisms, lower levels of contamination and the mixture of several contaminants may be more difficult to track but can result in pathologies from long term accumulation in the tissues of aquatic animals (Austin, 1998). A better understanding of specific pathological effects of pollutants enables us to pinpoint species and ecosystems that are most vulnerable to contamination and to distinguish pollutants that pose the greatest threats to the health of wild animals. A systematic focus on a specific physiological pathway from pollution to deterioration of the health of an organism might reveal similar patterns in a wider range of species and populations in contact with aquatic contaminants. For that, we need comprehensive reviews of the studies available on specific pathologies caused by contamination in aquatic ecosystems.

One of the pollution-induced pathologies that should be at the centre of attention in ecological and evolutionary research is cancer. Anthropogenic contamination has resulted in a rapid increase of both evolutionarily familiar and novel oncogenic substances in natural habitats, and presented animals inhabiting these environments with novel evolutionary pressures (McAloose & Newton, 2009; Giraudeau et al., 2018; Vittecoq et al., 2018). Whilst some oncogenic contaminants originating from natural sources have always been present in aquatic environments (Menzie et al., 1992), new substances have been added to this toxic cocktail, and the concentrations of oncogenic pollutants have reached unprecedented levels in many human-impacted habitats (e.g. Froehner et al., 2018). There are numerous examples of high mortality resulting from cancer in animals living in polluted aquatic environments such as, the high prevalence of intestinal adenocarcinomas in beluga whales (*Delphinapterus leucas*) from the Saint Lawrence Estuary (a highly polluted habitat due to effluents from aluminium smelting facilities, Martineau et al., 2002), the linking of cancer occurrence with organochlorine contaminants in California sea lions (*Zalophus californianus*, Randhawa et al., 2015), and the numerous discoveries of different types of fish tumours in polluted habitats (Brown et al., 1973; Black & Baumann, 1991). From a conservation perspective, understanding the leading causes for high rates of cancer within some wild populations allows us to better predict the vulnerabilities of wild populations to oncogenic contamination (McAloose & Newton, 2009). Some of the more prevalent aquatic contaminants with known oncogenic effects include persistent organic pollutants (for example polycyclic aromatic hydrocarbons (PAHs)), dioxins, polychlorinated biphenyls (PCBs), pesticides such as dichlorodiphenyltrichloroethane (DDT, Ashraf, 2017) and heavy metals (Tchounwou et al., 2012). The oncogenic effects of named pollutants might be further amplified by other characteristics of the Anthropocene, such as high levels of disturbance, climate change, introduction of novel pathogens, changes in food items, or genetic diversity level (Giraudeau et al., 2018). Considering the numerous examples of pollution-induced oncogenic processes in aquatic animals, in addition to other environmental and ecological processes that trigger neoplastic development (Thomas et al., 2017), we can expect that cancer is an underestimated cause of disease and mortality in many aquatic and semi-aquatic organisms living within human-impacted habitats. From the perspective of human health, studying the mechanistic links between pollution and cancer in non-model organisms, in an ecological context, provides a novel perspective for understanding eco-evolutionary processes linked to cancer at the cellular and organismal levels (Hamede et al., 2020).

A better understanding of the links between pollution and cancer in aquatic animals allows using wild species as sentinels for the contamination of aquatic environments with oncogenic chemicals for preventing an impact on human health, but also for preventing the negative effects of contamination on wild populations and ecosystems. Especially when

we consider that although mode and level of contamination may differ, similar mechanisms for cancer regulation and pathways for cancer initiation have evolved between vertebrate species, whether aquatic or terrestrial (for example: Schug et al., 2016; Dujon et al., 2020). This article combines the information available in the scientific literature about pollution and cancer in aquatic environments (see Tables 1 and S1) with the aim of addressing the following questions and proposing new research avenues. Using the available data, we predict which types of cancer aquatic pollution is more likely to cause and analyse the types of pollution currently associated with cancer in aquatic environments. We discuss the physiological mechanisms linking pollution and cancer, including main metabolic detoxification pathways, oxidative damage effects, infections, and changes in microbiome. Based on available studies, we describe which species are more vulnerable to pollution-induced cancer in aquatic environments and discuss which other species could be vulnerable based on analogy. We discuss the role played by pathogens and migration in exposing aquatic and semi-aquatic animals to oncogenic pollution. Finally, we suggest novel research avenues (Fig. 1), including the use of already published databases of gene expression levels in animals from differently polluted habitats.

## 2. What types of cancer does aquatic pollution cause?

Knowing where to look for cancer is one of the first challenges in measuring the extent to which populations are affected by pollution-induced cancer and understanding the mechanistic link between pollution and cancer. Humans are regularly exposed to oncogenic pollution, for example, through the air that they breathe. As a result, lungs are an organ that is commonly affected by pollution-induced cancer in humans (Kim et al., 2018). Similarly, in fish, organic pollutants are often absorbed through the gills and skin, and accumulate in lipid-rich tissues, such as liver, brain, gonads, and hypodermal lipid storages. Studies that link pollution and cancer in aquatic habitats indicate that skin cancer is a frequent outcome of living in contaminated waters, especially in several fish species (Table 1). For example, as a result of exposure to contaminants, freshwater drums (*Aplodinotus grunniens*) develop chromatophomas (Black, 1983), white suckers (*Catostomus commersonii*) and brown bullheads (*Ameiurus nebulosus*) develop papillomas (Sonstegard, 1977; Baumann et al., 1991), common dab (*Limanda limanda*) develop hypodermal lipomas and papillomas (Vethaak et al., 2009) and walleyes (*Sander vitreus*) dermal ossifying fibromas (Black et al., 1982).

The natural sources of oncogenic contaminants (Menzie et al., 1992), which have existed for hundreds of millions of years, have allowed fish and other organisms to develop various pathways to transform (like cytochrome p450 systems) or reduce (metallothioneins) the effects of these pollutants (Livingstone, 1998). Whilst xenobiotic metabolism protects the organism effectively from an array of lipid-soluble contaminants, in the case of some pollutants, such as PAHs, this process is responsible for the production of the highly reactive and genotoxic metabolites that lead to cancer development (Gao et al., 2018). In addition, chronic exposure combined with adverse environmental conditions can overwhelm these systems, causing severe malfunctions, including tumours. Accordingly, next to skin cancer, cancers of the liver, that assist in processing contaminants, are very common. Hepatic tumours have been described in many fish species including white suckers, brown bullheads, common dab, Atlantic tomcod (*Microgadus tomcod*), hagfish (*Myxine glutinosa*), English sole (*Parophrys vetulus*), winter flounders (*Pseudopleuronectes americanus*), and walleyes (references in Table S1). Similarly, other organs exposed to high concentrations of contaminants such as bile duct and kidneys are often affected by malignant processes, as seen in studies of white suckers (i.e. Blazer et al., 2017) and rainbow trout (*Oncorhynchus mykiss*, Shelton et al., 1983; Groff, 2004; Dale et al., 2009).

Interestingly, malignant tumours in lipid-rich brain tissues, which could be a promising future study direction (Fig. 1), are often under-described and under-studied throughout the literature. It is likely that

**Table 1**

Studies that link pollution to cancer in aquatic and semi-aquatic species. For an overview of all the studies published on cancer in aquatic and semi-aquatic species, please see Table S1. Scientific names have been updated with accepted names from WoRMS (WoRMS Editorial Board, 2020).

	Scientific name	Common name	Captive (C)/Wild (W)	Type of neoplasia	Pollution linked to cancer	Cancer prevalence	Other reference
Platyhelminthes	<i>Bdellocephala brunnea</i>	planaria	C	Undetermined neoplasia	Benzo(a)pyrene		Hoshina & Teshirogi, (1991)
	<i>Girardia dorocephala</i>	planaria	C	Undetermined neoplasia	Cadmium sulphate	3.4–14.7	Hall et al., (1986)
	<i>Girardia tigrina</i>	Dugesia tigrina	C	Undetermined neoplasia	Cadmium sulphate and 12-0-tetradecanoylphorbol-13-acetate (PMA)	30–90	Voura et al., (2017)
Mollusca	<i>Corbicula fluminea</i>	Asian clam	C	Undetermined neoplasia in digestive gland	Bisphenol A		Benjamin, Competente & de Guzman, (2019)
	<i>Crassostrea virginica</i>	Eastern oyster	W/C	Neoplasms in kidney, gastrointestinal tract, gonadal, gill, heart and neural elements and included carcinomas	PCB's, hydrocarbons (inc. PAH's), heavy metals (As, Cd, Cr, Cu, Pb, Mn, Ni)	7–14	Gardner & Yevich, (1988)
	<i>Mya arenaria</i>	Soft-shell clam	W/C	Disseminated neoplasia, gonadal neoplasia, haemocytic leukemia, seminomas and dysgerminomas	PCB's, pesticides (β-endosulfan and α-endosulfan), hydrocarbons (oil), PAH's, heavy metals	68–90	Reinisch et al., (1984); Muttray et al., (2012); Brown, (1980); Gardner et al., (1991); Böttger et al., (2013)
	<i>Mytilus edulis</i>	Blue mussel	W/ Farmed	Disseminated neoplasia/ haemocytic leukemia	Sewage, pulp mill effluents, metals	23–56	Charles et al., (2020); St-Jean et al., (2005)
	<i>Mytilus galloprovincialis</i>	Mediterranean mussel	Farmed	Gonadal neoplasia/ germinoma	Heavy metals, PCB's, PAH's	15–60	Ruiz et al., (2013)
Fish	<i>Ameiurus nebulosus</i>	Brown bullhead	W	Skin/liver neoplasms, cholangioma, hepatoadenoma, hepatocarcinoma, cholangiocarcinoma,	PCB, PAH	22–41	Baumann & Harshbarger, (1995); Baumann, (1998); Baumann & Harshbarger, (1998), Baumann et al., (1991)
	<i>Anguilla anguilla</i>	European eel	W	Undetermined neoplasia in liver and spleen	Pesticides, heavy metals, PAH's	30	Ribeiro et al., (2005)
	<i>Aplodinotus grunniens</i>	Freshwater drum	W	Chromatophoroma, neurolemmoma, carcinoma	PAH	16.67	Black, (1983)
	<i>Ameiurus melas</i>	Black bullhead	W	Oral papillomas	Chlorine	73	Grizzle, Melius & Strength (1984)
	<i>Catostomus commersonii</i>	White sucker	W	Hepatic neoplasm, hepatocellular carcinoma, bile duct carcinoma, papillomas,	Industrial pollution, PAH's	~60	Hayes et al., (1990); Sonstegard, (1977)
	<i>Danio rerio</i>	Zebrafish	C	Malignant neoplasms of the intestine, epidermal papillomas, Chondroma or chondrosarcoma, hepatic neoplasia, hemangioma, peripheral nerve sheath tumor, hemangiosarcoma, hepatocellular adenoma, hepatocellular carcinoma, biliary adenoma, biliary carcinoma, seminomas, adenocarcinoma, adenomas, leiomyosarcoma, rhabdomyosarcoma	PAH (7,12-Diniethylbenz[a]anthracene), Ethylnitrosourea, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)	16–100	Beckwith et al., (2000); Spitsbergen et al. (2000a, 2000b)
	<i>Fundulus heteroclitus heteroclitus</i>	Mummichog	W/C	Hepatoblastoma, hepatocellular adenoma, hepatocellular carcinoma, cholangiocellular proliferative lesions	PAH's inc. BaP	35	Wills et al., (2010); Vogelbein et al., (1990)
	<i>Hoplias malabaricus</i>	Trahira	W	Pancreatic neoplasia	Persistent organic pollutants,		Miranda et al., (2008)
	<i>Limanda limanda</i>	Common dab	W	Papillomas, hepatocellular adenoma, hepatocellular carcinoma	Cadmium, PCB's	20	Lerebours et al., (2014); Vethaak et al., (2009)
	<i>Microgadus tomcod</i>	Atlantic tomcod	W	Hepatic neoplasm; hepatocellular carcinomas	PAH/PCB/pesticides	44.3–92.9	Dey et al., (1993)
	<i>Myxine glutinosa</i>	Hagfish	W	Hepatocellular adenoma, hepatocellular carcinoma, cholangiocellular carcinoma, cholangiocellular adenofibrosis, mixed hepato- and cholangiocellular tumours	PCB's	5.8	Falkmer et al., (1978)
<i>Nibea mitsukurii</i>	Croaker	W	Chromatophoroma	Nifurpirinol	71–100	Kimura et al., (1989)	

(continued on next page)

Table 1 (continued)

	Scientific name	Common name	Captive (C)/Wild (W)	Type of neoplasia	Pollution linked to cancer	Cancer prevalence	Other reference
	<i>Oncorhynchus mykiss</i>	Rainbow trout	C/ Farmed	Hepatocellular carcinoma	PCB's/aflatoxin B1	40.2	Shelton et al., (1983)
	<i>Oryzias latipes</i>	Medaka	C	Cholangioma, hepatocellular carcinoma, hemangiopericytoma, perisinusoidal cell neoplasm, rhabdomyosarcoma	PAH's (BaP, DMBA)		Fabacher et al., (1991); Hawkins et al., (1990)
	<i>Parophrys vetulus</i>	English sole	W	Hepatocellular carcinoma, cholangiocellular carcinoma, adenomas	Creosote (aromatic hydrocarbons), PAH's	27	Malins et al., (1985); Malins & Haimanot, (1990)
	<i>Poecilia reticulata</i>	Guppy	C	Hepatocellular neoplasms	PAH's (BaP, DMBA)	19–46	Hawkins et al., (1990)
	<i>Pseudopleuronectes americanus</i>	Winter Flounder	W	Cholangiocarcinomas, hepatocellular carcinomas, hepatocellular adenoma, cholangioma, hepatic neoplasms	PAH/pesticides/metals	18	Chang et al., (1998), Gardner & Yevich, (1988)
	<i>Platichthys flesus</i>	European flounder	W	Cholangioma, hemangioma, carcinomas, adenomas, angiosarcoma, hepatoblastoma, mixed hepato-cholangio carcinoma, mixed hepatoangiosarcoma	PCB's, organochlorines	24–72	Köhler, Wahl & Söffker, (2002); Koehler, (2004)
	<i>Sander canadensis</i>	Sauger	W	Hepatocellular carcinomas, dermal ossifying fibroma	Metal (copper ores)	100	Black et al., (1982)
	<i>Sander vitreus</i>	Walleye	W	Hepatocellular carcinoma, dermal ossifying fibroma	Metals/PAH	<30	Black et al., (1982); Baumann, (1998)
Amphibians	<i>Rana pipiens</i>	Leopard frog	C	Sarcoma	3-methylcholanthrene (PAH)	9	Outzen et al., (1976)
Mammals	<i>Delphinapterus leucas</i>	Beluga	W	Adenocarcinoma, squamous cell carcinoma, granuloasa cell tumour, dysgerminoma, lymphosarcoma, neuroendocrine carcinoma, transitional cell carcinoma	PAH (BaP), PCB's (organohalogens)	18–24	Martineau et al., (1994); Martineau et al., (2002); Martineau et al., (1988)
	<i>Zalophus californianus</i>	California sea lion	W	Carcinoma	PCB's	18	Ylitalo et al., (2005); Randhawa et al., (2015)

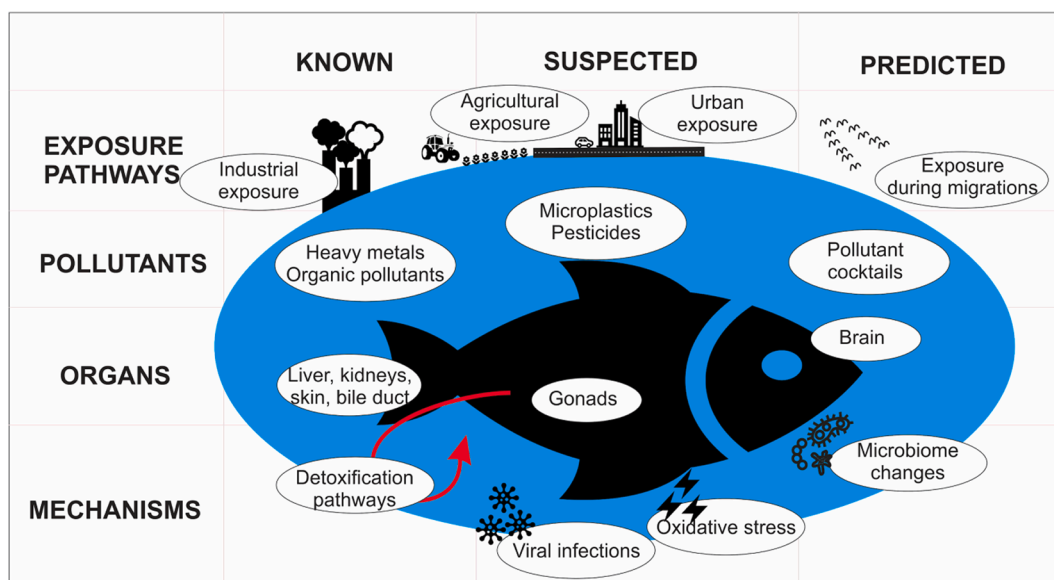


Fig. 1. Current known, suspected and predicted factors influencing cancer prevalence in aquatic environments.

in wild populations, tumour diagnosis is limited by specific types of analyses (e.g. histopathology from tissues most likely affected), causing bias in published studies. New molecular methods (e.g. biomarkers that are either specific or nonspecific to a certain tissue) could resolve this imbalance.

### 3. Which types of pollution are mainly associated with cancer in aquatic environments?

Increase in cancer prevalence can and has been linked to various types of pollution (Table 1), including organic pollutants (e.g. mutagenic PAHs, genotoxic persistent organic pollutants, POPs) and non-essential metallic trace elements (e.g. cadmium, arsenic). However, it

has been estimated that 100,000 new substances currently used on the European market can potentially end up in the environment and should therefore be considered as emerging pollutants (Brack et al., 2018). Developing our understanding of how this wide variety of pollutants contributes to cancer in aquatic species is paramount in understanding both how populations are likely to be impacted in polluted habitats and the biological mechanisms that initiate oncogenic processes with exposure (Table 2). However, the wide spectrum and low concentrations of these substances in the environment present challenges for understanding their effects on the health of aquatic organisms, especially, when such linkages between tumour prevalence and presence of potentially mutagenic toxicants are not always causal.

One finds the substances that one looks for – therefore it is important for (evolutionary) ecotoxicologists to assess the effects of groups of toxicants rather than limit interpretation to a specific chemical group, as is often the case in older studies. For example, the two most prominent groups studied (Table 1, Fig. 1) are PAHs and heavy metals, which have been widely described to co-occur in environments affected by anthropogenic pollution (e.g. Hsu et al., 2019; Monaco et al., 2017; Dai et al., 2020). These chemical ‘cocktails’ that are present in wild environments are known to have additive, synergistic or antagonistic effects (Laetz et al., 2009; Ansari et al., 2004). This synergism and antagonism can be further exacerbated when considering the effect of other environmental stressors resulting from climate change (see Crain et al., 2008). In addition, abiotic environmental stressors and physiological factors, such as ocean warming, that modify the bioavailability of pollutants (Parmesan & Yohe, 2003), or physiological responses to reproduction periods, that alter metabolism, could increase species sensitivity to mutagenic toxicants. Furthermore, some marine debris, specifically microplastic particles, are known to form biofilms, which could potentially act as a vector for increased oncogenic viral transmission (Cole et al., 2011) and can accumulate various aquatic contaminants (Ziccardi et al., 2016). Understanding the pathways that expose different species to a pollutant or group of pollutants is important in understanding whether certain species, for example benthic species that are exposed through sediment contact and trophic transfer (Sakurai et al., 2009; Cope et al., 2008), are more at risk from oncogenic contaminants (see Section 5). The bioaccumulation or biomagnification of pollutants and pollutant cocktails varies, not only between the type of contaminants but also, between the species, habitat and feeding habits of the animal exposed (Bakir et al., 2016).

However, there is still relatively little known about cocktail effects and the impacts of multiple environmental stressors, in relation to cancer development in natural environments. Based on the studies published so far, aquatic ecosystems in contact with organic pollutants or heavy metals should be the focus for the study of wildlife cancer, however, emerging contaminants should not be overlooked. Whilst there is currently only one study linking cancer in aquatic animals to pesticide exposure (Chang et al., 1998), this scarcity is probably not an indicator of a missing link, but rather of a study gap. Experimental studies would be necessary for disentangling the effects of individual pollutants on cancer development in aquatic species and in addition, longitudinal studies following the clean-up of polluted aquatic

environments, could be an underused opportunity for understanding which types of pollutants are mainly responsible for cancer in wild animals.

Cancer is a multifactorial disease and many pollutants do not directly cause cancer but alter biological systems that affect natural cancer defence mechanisms (eg. Schug et al., 2016). Whilst the mechanisms behind cancer initiation following pollution exposure (such as the formation of DNA adducts and the activation of specific genes), have been explored in some studies (Table 2) we suggest that this is an important research area that needs further attention in the future.

#### 4. Physiological mechanisms that link pollution and cancer

##### 4.1. Metabolic pathways connecting pollution and cancer

The precise mechanistic cause and effect relationship connecting environmental pollution and cancer, specifically at the subcellular/molecular level, is still uncharacterized (Lerebours et al., 2014). Therefore, studies exploring this concept would provide a background knowledge of the metabolic processes that, with exposure to pollution, could increase cancer risk within aquatic populations. In the context of toxicological effects, aryl hydrocarbon receptor (AHR, AhR, AH-r, or Ah-r as used in different publications) expression is probably one of the most researched pathways that plays a pivotal role in detoxification processes in aquatic animals (e.g. Zhou et al., 2010). The expression of AHR, a ligand-activated nuclear transcription factor, can be altered through exposure to a variety of environmental contaminants such as POPs (including PAHs and halogenated aromatic hydrocarbons, HAHs, Zhou et al., 2010). A recent study suggests that the desensitization of AHR pathway genes in gulf killifish (*Fundulus grandis*) can help individuals cope with heavy urban pollution load (PAHs and HAHs) in Galveston Bay, USA (Oziolor et al., 2019). We hypothesise that there are similar downregulation mechanisms in other aquatic species to potentially protect cells from oncogenic contaminants.

The induction of synthesis of heat shock proteins (HSPs) as a response to any kind of environmental stress (temperature, salinity, hypoxia, chemicals, etc.) has been demonstrated in all organisms examined to date, from prokaryotes to humans, and could constitute a link with cancer. For example, both histopathological alterations and a significant increase in HSP70 expression in milk fish (*Chanos chanos*) were found at a site polluted with heavy metals when compared to a ‘less’ polluted site in India (Rajeshkumar & Munuswamy, 2011). Evidence supports that HSPs are likely to have anti-apoptotic properties and are actively involved in tumour cell proliferation, invasion, differentiation, metastases and death. Whilst there have been some studies suggesting increased expression of HSP’s in fishes with exposure to pollution, more research is needed to understand the links between HSP expression and cancer in aquatic animals.

Endocrine disruption has been evidenced to occur as a result of exposure to some environmental pollutants (eg. pesticides) (Soto & Sonnenschein, 2010). These chemicals bind to endocrine receptors and alter the hormonal response which are known to control cancer initiation in humans (Schug et al., 2016). The endocrine system controls a

**Table 2**

Studies that have linked aquatic pollutants and cancer in wild animals through a specific physiological mechanism.

Pollutant type	Suggested mechanism	Species	References
PAH (BaP)	EROD activity/Mitochondrial DNA damage	Mummichog ( <i>Fundulus heteroclitus</i> )	Wills et al., 2010
PAH/PCB/pesticides	Activation of K-ras oncogene/DNA lesions	Atlantic tomcod ( <i>Microgadus tomcod</i> )	Wirgin et al., 1989; Cormier et al., 1989
PAH	Genotoxicity	Winter Flounder ( <i>Pseudopleuronectes americanus</i> )	Baumann 1998,
PAH (BaP), PCB's (organohalogens)	Immunosuppression, DNA adducts	Beluga ( <i>Delphinapterus leucas</i> )	Martineau et al., 1994
Cadmium	Pollutant-induced mutational activation/inactivation of key genes (Rb genes)	Common dab ( <i>Limanda limanda</i> )	Lerebours et al., 2014

number of biological processes in all vertebrates and whilst disruption has been linked to cancer in humans and rodents, it is likely that these chemicals also play an underestimated role in cancer initiation in aquatic animals (Schug et al., 2016)

#### 4.2. Cancer induction by oxidative stress and DNA damage pathways

As aquatic animals are arguably exposed to a greater quantity and variety of pollutants than terrestrial animals, they present good opportunities to understand the link between pollution and cancer at the cellular level. A broad spectrum of pollutants can compromise the genomic integrity of cells by inducing DNA damage or by generating oxidative stress (Rastogi et al., 2010; Lerebours et al., 2013; Rhee et al., 2013). DNA damage plays a key role in mutagenesis and the development of cancer (Rotchell et al., 2001; Du Corbier et al., 2005; Lerebours et al., 2014, 2017). Certain PAHs have the capacity to enter redox cycles and induce the production of reactive oxygen species (ROS), thereby causing oxidative stress (An et al., 2011). Some benzo(a)pyrene (BaP) metabolites can undergo redox-cycling, producing ROS thereby leading to DNA damage (Chatgililoglu and O'Neill, 2001) and mutations (Bonner et al., 2005).

Considering this importance of oxidative stress and DNA damage in initiating oncogenic processes, and the impact of carcinogens on these processes, it is surprising that the link between exposure to carcinogens, oxidative stress, DNA damage and neoplasia has been scarcely addressed in aquatic organisms. A clear relationship between oxidative DNA damage and neoplasia was evidenced in feral English sole exposed to PAHs from Eagle Harbor, U.S. (Malins et al., 1985). Interestingly, an increase in antioxidants (such as superoxide dismutase, catalase and glutathione) has been observed in long-lived aquatic organisms such as in the mud clam (*Arctica islandica*) and the red-eared slider turtle (*Trachemys scripta elegans*) (for a review see Wojtczyk-Miaskowska & Schlichtholz, 2018). This suggests that the antioxidant system confers cell survival by preventing ROS-induced DNA damage and subsequent cancer development.

Depending on the type of DNA damage induced, several DNA repair mechanisms are triggered to maintain genomic stability. However, some of them are more prone to errors and are often associated with cancer. PAHs, specifically BaP metabolites, can form DNA adducts that cause errors in DNA replication during DNA repair (Boelsterli, 2007; Phillips & Arit, 2007). Exposure to PAHs has been firstly, linked to an increase in DNA adducts in the pale chub (*Zacco platypus*) (Lee et al., 2014), killifish (*F. grandis* and *F. similis*) (Willett et al., 1995) and Beluga whales (Mathieu et al., 1997) and secondly, correlated to DNA adduct formation and neoplastic lesions in fish such as brown bullhead (Ploch et al., 1998) and English sole (Reichert et al., 1998) and marine mammals such as harbour porpoises (Acevedo-Whitehouse et al., 2018) and beluga whales (Poirier et al., 2019). In order to further explore these cause-effect relationships, studies should consider oxidative stress and DNA damage/repair biomarkers, histopathological conditions and a high number of carcinogens (including metabolites) together in environmental scenarios, where aquatic organisms are often exposed to a mixture of pollutants.

#### 4.3. Interactions between the gut microbiota and pollutants and consequences for cancer development

The microbiome is essential for major biological functions, including the biotransformation of xenobiotics (Sousa et al., 2008; Jandhyala et al., 2015) and the control of cancerous processes (Elinav et al., 2019). A disruption of the microbiota balance, named dysbiosis, leads to the alteration of the functioning of the gut microbiome and could result in cancers (Scanlan et al., 2008; Meng et al., 2018, Fig. 1). Many pollutants such as metals (cadmium, lead, arsenic), pesticides (DDT, chlorpyrifos, glyphosate) and PCBs have demonstrated their ability to cause quick microbiome dysbiosis, affecting both the microbiota composition and

also the microbiota metabolic functions, mainly in vertebrates and through trophic transfer (Flandroy et al., 2018).

Microbiota also has, in some cases, the capacity to influence pollutant behaviour and ultimately their molecular and physiological effects (Dietert & Silbergeld, 2015). Gut microbiota has been known for a long time to be involved in biotransformations of xenobiotics through various mechanisms (Scheline, 1973; Sousa et al., 2008; Kang et al., 2013; Claus et al., 2016). However, the few enzymes that have been recognized to play a role in these transformations have mainly been studied in humans (Eriksson & Gustafsson, 1970; Williams et al., 1970; Bakke & Gustafsson, 1984; Rafil et al., 1991; Roldán et al., 2008). Many carcinogenic pollutants metabolized by gut microbiota, mainly in vertebrates, include PAHs (benzo(a)pyrene), nitrated PAHs, nitrotoluenes, pesticides (DDT), PCBs and metals (mercury, arsenic) (Claus et al., 2016).

Hence, microbiota can on one hand interact with environmental pollutants (microbiota can modify the cycle and thus the toxicity of pollutants that in turn affect the microbiota composition) and on the other hand modulate cancer development. Thus, one can predict that gut microbiota could be a major driver in the processes leading to cancer emergence in aquatic organisms that have been chronically exposed to a cocktail of contaminants. Therefore, microbiota could be considered as a promising biological indicator of the organism's health status and, accordingly, more attention should be focused on the microbiota in future wildlife cancer studies.

### 5. Evidence of cancer in animals living in (polluted) aquatic environments

Understanding the reasons for cross-species variation in cancer development as a result of exposure to pollution promises extremely valuable information on oncogenic processes, as the limited research conducted on non-standard model organisms has already provided tremendous insights on the natural mechanisms of cancer resistance. Despite its value, robust cancer prevalence data on animals is surprisingly limited to date, currently only available for 31 wild vertebrate species (Ujvari et al., 2017). The latter database indicates stunning cross-species variation of cancer rates in aquatic and semi-aquatic species with less than 1% of the sea otters (*Enhydra lutris*), 23% of white-fronted geese (*Anser albifrons*) and 64% of the gray seals (*Halichoerus grypus*) developing some type of cancer (Ujvari et al., 2017). To compare, the general estimates for a lifetime risk for cancer in humans is around 40% (e.g. Grunau et al., 2018). While cancer prevalence data is extremely limited, there is more information available on cancer occurrences across wild species. Considering that the representation of aquatic species in cancer studies is impressive. There have been reports of neoplasia in over 330 aquatic species and a variety of studies that link cancer to contaminant exposure (Table S1). However, there are challenges to fully understanding the role pollution plays in inducing cancer, such as the dynamic nature of cancerous cell development, multiple contributing factors to neoplasia development in natural environments and ethical concerns in cancer diagnosis in wild animals. Histopathology (Box 1), through dissection, is currently the most reliable method used to measure cancer prevalence. This has likely contributed to the study bias towards fish and bivalves in pollution-induced cancer studies (Fig. 2). However, given the range of taxa that have shown susceptibility to pollution-induced neoplasia, the literature indicates that this phenomenon might affect a much wider range of species than originally considered.

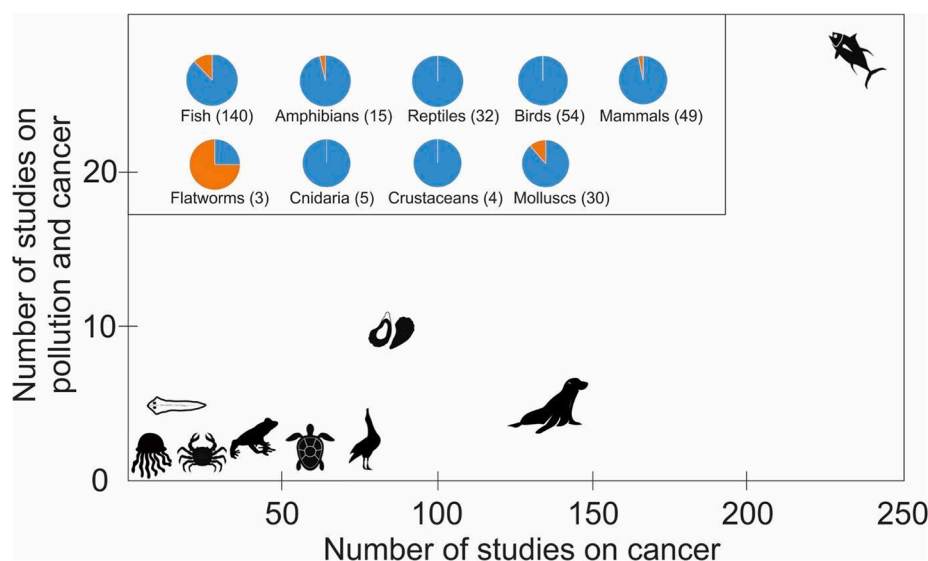
#### 5.1. Invertebrates

##### 5.1.1. Platyhelminthes

Three species of planaria (*Dugesia tigrina*, Voura et al., 2017 (accepted as *Girardia tigrina*, WoRMS Editorial Board, 2020), *Dugesia dorotocephala*, Hall et al., 1986 (accepted as *Girardia dorotocephala*,

**Box 1**  
Glossary of terminology

Term	Definition
Neoplasia	The formation of a new, abnormal growth of tissue
Tumour	Either a benign or malignant, abnormal growth of tissue that leads to a swelling in an area of the body
Cancer	A malignant growth or tumour resulting from uncontrolled cell division
Histopathology	The study of changes in tissues as a result of disease
Disseminated neoplasia	A leukemic-type process which is characterized by the excessive proliferation of haemolymph cells and their dissemination in the circulatory system
Omics data	Comprehensive data that aims to build complete genetic and/or molecular profiles of an organism



**Fig. 2.** Number of studies that indicate cancer in aquatic and semi-aquatic species, and number of these studies that link cancer occurrence to pollution. Groups of animals depicted in this figure include (from left) cnidarian, flatworms, crustaceans, amphibians, reptiles, birds, molluscs, mammals, and fish. Position of the picture indicates the number of studies on this group. Pie charts illustrate proportions of pollution-associated studies per group, numbers in brackets indicate the number of species studied so far.

WoRMS Editorial Board, 2020) and *Bdellocephala brunnea*, Hoshina & Teshirogi, 1991) have shown evidence of pollution-induced neoplasia (Table 1). Interestingly, *G. tigrina* has more recently been used as a model species for cadmium oncogenesis to better understand the mechanisms leading to cancer development (Voura et al., 2017). Using planaria, with their known regeneration capabilities, could provide a deeper understanding of cancer in humans and lead to potential therapies to improve survival (Oviedo & Beane, 2009).

**5.1.2. Cnidaria**

A range of cnidaria species have shown evidence of neoplasia development from hydra to *Acropora* corals, however, currently there have been no conclusive studies linking neoplastic development in cnidaria to pollution within the literature. *Hydractinia echinata* showed evidence of induced neoplasms under experimental conditions (Millane et al., 2011) and whilst there have been several reports of tumours on coral species in natural environments (Sutherland, Porter & Torres, 2004), only two cases have diagnosed these tumours as neoplastic (Table S1). Peters, Halas & McCarty, (1986) diagnosed nodules on *Acropora palmata* colonies as calicoblastic epitheliomas. The second study diagnosed calicoblastic epitheliomas in *Acropora valenciennesi* and found similar tumours in the species *Acropora valida*, although the latter species were not diagnosed using histopathology. A study on *Porites* sp., that found tumour prevalence as high as 39.1% in one of the surveyed locations, found a correlation between distance from the local city and percentage of evident tumours (Kaczmarek, 2006). The authors suggested coastal pollution as a possible cause, although this was not tested.

**5.1.3. Molluscs**

The majority of studies on neoplasia in invertebrates have focused on molluscs (Table S1, Fig. 2), potentially because many species within this phylum are widely farmed and consumed by humans. There are two main types of neoplasia reported in bivalves; disseminated neoplasia (DN, see Section 6) and gonadal neoplasia (Table S1). There is evidence that exposure to pollution can increase cancer prevalence in a range of species (Table 1). For example, exposure to PCB's resulted in cancer rates of up to 90% of a population of soft-shell clams (*Mya arenaria*) (Reinisch et al., 1984). Furthermore, cancer was induced in 14% of oysters (*Crassostrea virginica*) exposed to contaminated sediments in a laboratory experiment (Gardner & Yevich, 1988). Cancer rates reduced to 7% in caged individuals placed in natural environments.

Intriguingly, disease prevalence can differ between farmed and wild populations of molluscs due to population density (Morley, 2010). Farmed molluscs are often in greater population densities and could therefore be at more risk of neoplastic development, especially due to the transmissible nature of cancer in some bivalve species (Morley, 2010). Most molluscs are sedentary, so aquatic pollution could pose a significant risk to a number of species. In addition, the bioaccumulation of oncogenic pollutants, such as cadmium, within the tissues of bivalves (e.g. Rumisha et al., 2012), could increase cancer development in some mollusc communities.

**5.1.4. Crustaceans**

Whilst neoplasia has been recorded in very few crustacean species (Table S1) and pollution-induced cancer has not been recorded,



histopathological cell changes, suggesting first stages of hemic neoplasia development, have been recorded in the tropical crab (*Paratelphusa hydrodromous*) with exposure to cadmium chloride (Victor, 1993). This suggests that this species could be susceptible to pollution-induced cancer. However, further research is needed to determine whether these cell changes develop into neoplastic lesions and therefore whether this species, and others, are susceptible to pollution-induced cancer.

## 5.2. Vertebrates

### 5.2.1. Fish

There have been three main approaches used in fish-based oncogenic studies. Firstly, a number of studies compare the contaminant concentration within the tissue or bile with the rate of neoplasia. Examples of species studied include common dab, winter flounder and European eel (*Anguilla anguilla*). These studies have shown evidence of pollution-induced cancer resulting from exposure to contaminants, such as PAHs, pesticides and metals (Lerebours et al., 2014; Chang et al., 1998; Ribeiro et al., 2005). Secondly, studies have tested for a relationship between the levels of contaminants in the sediments and cancer prevalence. Baumann & Harshbarger (1998) have, for example, shown that reductions in the levels of PAHs in sediments, following the closure of the local coking plant, led to a significantly lower percentage of neoplasia in brown bullheads (*Ameiurus nebulosus*). Thirdly, experimental studies in captivity have been used to determine susceptibility to carcinogens, mostly using model species. For example, zebrafish (*Danio rerio*) have been exposed to known carcinogens in laboratory experiments (Beckwith et al., 2000; Spitsbergen et al., 2000a; Spitsbergen et al., 2000b).

A few studies have combined the first two approaches by measuring contaminant concentrations in both sediments and fish tissue or bile samples (e.g. Baumann et al., 1991; Malins et al., 1985). This has the potential to develop our understanding of pathways of carcinogens and whether high levels of contaminants in sediments predict the concentrations within an organism and therefore the potential increased risk of neoplasia. For example, Sakurai et al., (2009) exposed marbled sole (*Pleuronectes yokohamae*) to a range of contaminants in bottom sediments and food sources of fish, showing that dichlorodiphenyldichloroethylene (DDE) is transferred in higher concentrations through the sediment whilst DDT was transferred through the food. The different pathways in chemical absorbance increase the challenge in understanding the risk of carcinogen-induced neoplasia in aquatic species. Many of the fish species in Table 1 are benthic species and are at greater risk from contaminant uptake through both the sediment and trophic transfer (Fan et al., 2017). The bioaccumulation and biomagnification of contaminants up trophic levels could further increase the risk of demersal fish to pollution-induced neoplasia (Kelly et al., 2007).

There are many challenges in developing a clear understanding of how susceptible fishes are to pollution-induced neoplasia. For example, Atlantic tomcod showed increases in liver neoplasia from 3 to 10% at 'clean' sites to 44–93% at 'polluted' sites (Dey et al., 1993). However, no significant relationship between the levels of individual pollutants and the prevalence of neoplasia was found. This suggests that either antagonistic or synergistic effects of contaminants (see Section 3) play a role in increasing the toxicity of individual contaminants (Hartl, 2002) or that other biological or environmental factors are causing the increase of neoplasia measured in these polluted systems. Interestingly, Atlantic tomcod have shown evidence of developing a resistance to some pollutants, including PCB's, thereby reducing their cancer risk (Wirgin & Waldman, 2004). Understanding which species can adapt to anthropogenically impacted environments, and the mechanisms for this adaptation, could give useful insight into oncogenic evolution (Vittecoq et al. 2018).

### 5.2.2. Amphibians

As many amphibians are semi-aquatic they could be susceptible to

increased neoplasia prevalence from aquatic pollution exposure. Different types of cancer have been diagnosed in amphibians, for example, carcinoma in the common frog (*Rana temporaria*) and lymphosarcoma and leukaemia in the alpine newt (*Ichthyosaura alpestris*) (O'Brien et al., 2017) (See Table S1). In addition, Outzen et al., (1976) induced sarcomas in leopard frogs (*Rana pipiens*) using the carcinogenic PAH, 3-methylcholanthrene. Furthermore, the marsh frog (*Rana ridibunda*) showed histopathological alterations, diagnosed as early stages of holangiofibroma development, from a polluted river in northern Greece whereas no histopathological alterations were observed in frogs from a clean river (Loumbourdis, 2007). Loumbourdis, (2007) suggested that heavy metals, such as cadmium, were involved in the histopathological changes observed in frogs in polluted rivers. Therefore, it is possible that pollution in freshwater environments could increase cancer rates in frogs

### 5.2.3. Reptiles

Cancer in aquatic and semi-aquatic reptiles has been shown to affect a range of species including snakes, turtles, crocodiles and lizards. Studies on green turtles (*Chelonia mydas*) are the only species researched that suggests a link between cancer and pollution. Although it is widely accepted that fibropapillomas in turtles result from infection with chelonid herpesvirus 5 (Jones et al. 2016), a number of studies suggest a positive association between neoplasia development and pollution (Adnyana et al., 1997; dos Santos et al., 2010; Van Houtan et al., 2014; Foley et al., 2005). For example, dos Santos et al., (2010) used an ecological index to determine water quality in an area and found an increase in fibropapillomas from 0% in clean waters to 58.8% at polluted sites. In addition, as neoplasia development is often a multifactorial problem, it is possible that aquatic pollution could be working in concert with the viral etiology, resulting in increased neoplasia prevalence (see Section 6) (Ujvari et al., 2017, Chapter 3).

### 5.2.4. Birds

Studies have observed that aquatic birds develop cancer (Table S1), however, there has been little focus on how aquatic pollution influences the occurrence of neoplasia. As dissection is required for tissue collection for histopathology analysis, it is understandable why many aquatic bird species, which are often protected by law, have not been targeted to determine cancer prevalence across a population. Bioaccumulation and biomagnification of pollution in aquatic birds has been studied extensively and can impact the health of species differently depending on their ability to eliminate, metabolise and store contaminants (e.g. Tsygankov et al., 2016; Mwangi et al., 2016; Borgå et al., 2007; Albanis et al., 1996). Furthermore, many aquatic birds are at the top of their food chain making them susceptible to high levels of pollution through trophic transfer (Burger & Gochfeld, 2002; Romero-Romero et al., 2017). As aquatic birds are susceptible to cancer and the accumulation of contaminants linked to cancer prevalence in other species (Table 1), it is reasonable to assume birds inhabiting aquatic environments could be affected by pollution-induced cancer.

### 5.2.5. Mammals

Two species of marine mammals have shown evidence of pollution-induced neoplasia. An isolated population of Beluga whales in the St. Lawrence Estuary, Canada showed higher rates of cancer, due to benzo (a)pyrene exposure present in sediments, than Arctic populations (Martineau et al., 2002). As belugas feed on benthic organisms (Martineau et al., 2002) both trophic transfer and regular contact with polluted sediments could increase their exposure to oncogenic contaminants. Cancer in Californian sea lions has been suggested to be influenced by a range of factors including genetics, environmental contaminants and infectious disease (Browning et al., 2015). Although carcinomas in Californian sea lions have a viral etiology, specifically the otarine herpesvirus-1 (Buckles et al., 2006), another study found a positive relationship between PCB concentration in sea lion blubber and

carcinoma rates (Ylitalo et al., 2005). Many persistent pollutants, such as PCBs, have been shown to bioaccumulate and bio-magnify up trophic levels, increasing the risk to marine mammals of accumulating high concentrations of organic contaminants within their tissue (Jepson & Law, 2016).

Table S1 shows that neoplasia can occur in a range of other marine mammals, therefore it is possible other species are at risk from pollution-induced cancer. However, further work is required to determine whether mammal species in coastal areas, such as the Californian sea lions and beluga whales are more vulnerable to pollution-induced cancer than species that live further offshore, or whether current research efforts have simply been limited to these two species.

## 6. Characteristics of aquatic animals that may affect cancer prevalence

### 6.1. Vulnerability to pathogen-induced and transmissible cancers

Cancers with infectious causations have been extensively studied in humans (where 15–20% of cancers are supposed to be initiated and/or caused by infectious agents) and domestic animals but are much less understood in wild animals (Ewald & Swain Ewald, 2015). Several cases of virus-induced cancer have been detected in marine and freshwater vertebrates including, for example, those caused by papilloma viruses in sperm whale (*Physeter macrocephalus*, Lambertsen et al., 1987), Burmeister's porpoise (*Phocoena spinipinnis*, Van Bressem et al., 2007) and beluga whale (De Guise et al., 1994), by herpes virus in California sea lion (King et al., 2002) and green turtles (Lu et al., 2000) or by retrovirus in walleye fish, (Martineau et al., 1992) or Atlantic salmon (*Salmo salar*, Paul et al., 2006). Similarly, neoplasia with infectious causation have been detected in aquatic invertebrates such as flatworm (Tar & Torok, 1964), shrimps (Lightner & Brock, 1987) or hydra (Domazet-Lošo et al., 2014; Rathje et al., 2020).

Some pollutants have the potential to influence the dynamic of oncogenic processes caused by infectious diseases through their immune-suppressive effects but, surprisingly, only a handful of studies have investigated how environmental pollutants might influence the prevalence or severity of these cancers. The results of these studies (for example, Californian sea lions (Ylitalo et al., 2005) and green turtles (Foley et al., 2005)) show a general trend toward an increase of cancer prevalence in polluted habitats. Interestingly, this pathology has also been associated with the distribution of toxic benthic dinoflagellates (*Prorocentrum* sp.) of the Hawaiian Islands, through the production of a tumour-promoting toxin, okadaic acid (Landsberg et al., 1999). There is thus a need for more studies investigating the complex relationships between infection, cancer and the multitude of chemicals polluting freshwater and marine habitats. A crucial aspect to consider, that has been ignored so far, is the impact of pollution on the survival of the infectious agents and then on their transmission rate between hosts (Morley, 2010). Previous studies on pathogens, unrelated to oncogenic processes, suggested that both these essential fitness-related traits of virus biology might be impacted differently depending on the contaminants present in the environment (Chou et al., 1998; Kocan et al., 2001). In addition, by impacting host density through their effects on survival, reproduction and host population dynamic, pollutants have the potential to also influence the transmission rate of oncogenic pathogens, but this aspect has, to the best of our knowledge, never been studied.

In addition to virus-induced cancer, transmissible cancers show a similar potential to being affected by pollution. To date, nine transmissible cancers have been detected, with most of them recorded in marine ecosystems (Metzger et al., 2015). In marine habitats, horizontal transmission of malignant cells has been demonstrated in soft-shell clams (*M. arenaria*), mussels (*Mytilus trossulus*, *M. edulis*, *M. chilensis*), cockles (*Cerastoderma edule*), and inter-species contagion was observed in golden carpet shell clams (*Polittapes aureus*) where the cancer cells derived from another species, the pullet shell clam (*Venerupis corrugate*)

(Metzger et al., 2016). In all these cases, transmissible cancer manifests itself in the form of DN, and has, in some cases led to the death of a significant part of the population (Dujon et al., 2020).

The importance of pollution on DN prevalence or transmission has not been deeply investigated so far, but the impact of several chemical pollutants on DN in several host species has been assessed, mostly through correlative studies where sample sizes and/or chemical measurements are not sufficient to draw firm conclusions. This literature (reviewed in Carballal et al., 2015) has shown mixed results and has been published before the finding that DN could be characterized as a transmissible cancer in some species. We thus call for more studies on this topic in order to predict and potentially prevent future DN outbreaks in an increasingly polluted marine habitat.

### 6.2. Migration and cancer

Aquatic organisms, more often as a rule than an exception, undertake migrations of some extent during their ontogeny and thus it is likely that the environmental conditions in those different habitats shape individual life history. Fish species that are generally considered sedentary (e.g. coastal flatfishes) as adults, may still make movements of considerable distances. For instance, European flounders (*Platichthys flesus*) can undertake migrations up to 80–95 km with the longest recorded migration reaching approximately 700 km (Ojaveer & Dreves, 2003). Therefore, it can be expected that individual fish may encounter different contaminant levels during their migration (*sensu lato* – including mass movements between nursery and breeding grounds but also larval drift and individual short-range feeding migrations) over patchy environments. Marine top predators, such as marine mammals and seabirds, are at risk of accumulating the highest levels of pollutants. These species travel hundreds to thousands of kilometres every year to commute between their breeding and wintering grounds, and like fish species, are thus exposed to a wide range of pollutants along their annual cycle. For instance, great skuas (*Stercorarius skua*), breeding in the pristine Arctic, overwinter along industrialized coasts of Europe, North Africa and North America where accumulated concentrations of POPs might affect some populations (Leat et al., 2013). Similarly, mercury concentrations accumulated by little auks (*Alle alle*) are up to four times higher during their winter spent off Newfoundland than when breeding in Greenland (Fort et al., 2014). Whether or not this seasonal contamination can increase the risk of cancer still needs to be investigated, especially in species where pollutants are already known to have dramatic impacts on individuals and populations (Desforges et al., 2018).

Migration has received most attention in the form of studies on biomarker-based biological effect assessments, where the migrations have been considered as confounding factors that lead to a decrease in the bioaccumulation and biological effects of contaminants (Cooreman et al., 1993; Kirby et al., 1999; Kirby et al., 2000) and influence the variation in prevalence of pollution-induced cancer between different regions, sexes and age groups (Vethaak et al., 2009). However, it has to be kept in mind that migrations can result both in the dilution of pollutants when moving to cleaner environments (e.g. Kirby et al., 2000) and in contamination of animals when moving to or through more polluted areas (Vethaak et al., 2009).

Observations of a causal link between migratory patterns, pollutants and cancer is challenging as it requires determining where individuals get contaminated during different seasons, the levels of pollutants specifically accumulated within each occupied habitat and how each contributed to cancer. Therefore, for species that migrate to cleaner environments, the time elapse between exposure and capture could enable the organism to neutralize (e.g. detoxification pathways, DNA repair systems) the effects of the contaminants (Kirby et al., 2000). Whilst recent advances in the methods for describing individual migrations (e.g. Campana, 1999; Hussey et al., 2015; Kays et al., 2015) and potential exposure sources (e.g. Carr et al., 2017) have improved, the causal links between migration patterns and exposure to contaminants,

and subsequent carcinogenic impacts still lack demonstration. For instance, in a case study on a white sucker migration route, only sex and age of individuals, and not the sampling site could be statistically linked to the prevalence of neoplasia (Hoffman et al., 2020). Thus, in future work, simultaneously utilizing methods for detailed description of individual movements (e.g. otolith microchemistry, animal-borne tracking devices) and contaminant exposure (e.g. stable isotope analysis) should be used to describe how individual migrations may influence variations in contaminant-related cancer prevalence in aquatic organisms.

## 7. Potential of “omics” databases

Ecotoxicology research has produced a considerable amount of “omics” data (Martyniuk & Simmons, 2016). Researchers exposing various model and non-model organisms to tumour inducing chemicals have only occasionally explored the data in the context of cancer. A search in the NCBI Gene Expression Omnibus (GEO) DataSets with the keywords (pollution OR toxicology) AND (fish[organism]) AND (carcino\* OR cancer OR tumor OR neoplas\*) gave 5 results (4 non-redundant) while excluding the last search criteria returned 250 datasets. An equivalent query in the EMBL-EBI ArrayExpress returned 1 and 34 matches, respectively. Even more data can be found with manual scanning of papers in the field of toxicogenomics. For example, pentabrominated diphenyl ether, a cancer inducing pollutant (Dunnick et al., 2018), when used in an exposure experiment on European flounder, produced a time series of gene expression data (Kuiper et al., 2008; Williams et al., 2013), that was not included in the above NCBI or ArrayExpress search results. However, these datasets could constitute a valuable resource to discover potential early signs of cancer progression.

Most commonly, the detection of physiological mechanisms responsible for tumour progression has relied on pathway analysis on the set of differentially expressed genes (eg. Hummerich et al., 2006). In essence, this analysis workflow encompasses transcript assembly and annotation, pathway enrichment analysis and interpretation of the results. Proper transcript annotation is beyond the scope of this article, but it should be noted that reviewing annotations for old sequencing data from non-model organisms might be needed. The first step for pathway analysis might be finding the human orthologues of the genes, as non-human pathway databases are still incomplete (Rahmati et al., 2020). One way to find orthologues is to use the Ensembl Biomart orthologue filter. For non-model organisms, tools like OrthoDB (Kriventseva et al., 2019), OrthoFinder (Emms & Kelly, 2015) or JustOrthologues (Miller et al., 2019) could be used. In addition, tools like g:Profiler (Raudvere et al., 2019), pathDIP (Rahmati et al., 2020), DAVID (Huang et al., 2009) or pathfindR (Ulgen et al., 2019) enable finding cancer related pathways in the dataset. Arguably, the most important databases for finding cancer related genes from published pollution related data are Atlas of Cancer Signaling Network ACSN (Kuperstein et al., 2015) and COSMIC Cancer Gene Census (Sondka et al., 2018). An example of using the COSMIC database on non-model organisms can be found in a recent paper on seabirds (Meitern et al., 2020). However, the biggest challenge in such database comparisons is forming sensible hypotheses about tumour evasion mechanisms and validating them experimentally.

## 8. Synthesis and future avenues

Apart from climate change and over-exploitation, pollution presents one of the critical challenges for marine and freshwater ecosystems (Häder et al., 2020). Furthermore, cancer has been linked to pollution, so far, in around 30 aquatic species (Table 1). Pollutants can suppress the host immune system and thus increase the susceptibility of organisms to cancer-causing pathogens and/or the long-term accumulation of pollutants and tissue damage in organs and thus, initiate oncogenic processes. Migration and position in the food chain also influence individual levels of contaminant accumulation (Fig. 1).

It is evident from the literature that there has been a bias towards cancer studies in fish compared to other groups of species (Fig. 2). We suggest that this bias needs urgent addressing with future studies focusing on other species’ groups such as birds, amphibians and invertebrates. In order to include a wider range of species in the study of aquatic pollution and cancer, it is important to recognise the need for novel biomarkers and less invasive methods of cancer diagnoses other than histopathological analysis of carcasses (which we predict will still be the main reliable approach in the short run). The development of biomarkers such as those proposed in Table 3 could be one approach to solve this problem. These biomarkers have been linked to both cancer and pollution in a range of species, but whether they could be reliably used as a biomarker for cancer prevalence in a population, across numerous species, remains to be determined. Moreover, whilst skin and gills have been reported as the organs suffering more frequently from malignancies in aquatic species (Table S1), this could be because non-lethal sampling of the malignant tissue can be employed, compared to other lipid-rich tissues and organs related to xenobiotic metabolism, which would require sacrifice.

Freshwater environments could be an easy target for developing our understanding of how pollution induces neoplasia, by using restoration projects as natural experimental study systems. Determining cancer prevalence in a population prior to and following ecosystem restoration could provide new case studies for how species’ physiological and life-history trade-offs are impacted by cancer. A similar approach was used to show reduced neoplasia in brown bullheads following the closure of a coking plant (Baumann & Harshbarger, 1995). Therefore, we argue that utilizing restoration projects could help to bridge some of the gaps in current knowledge for pollution-induced cancer, particularly for other groups of species such as invertebrates and amphibians.

The past centuries have already seen the release of a large variety and quantity of chemical pollutants, with estimates predicting that 100,000 new substances currently used in Europe may become future pollutants, entering the food chain (Brack et al., 2018) and accumulating in high concentrations in some individuals, populations or species (e.g. UN Environment, 2019; Jones & De Voogt, 1999). Understanding the combined impacts of environmental parameters and pollution cocktails on cancer prevalence is an area that needs urgent research. For example, various pollutants may simultaneously accumulate in the same organisms that might also face rising water temperatures and elevated exposure to oncogenic viruses/pathogens, resulting in a cascading event that could lead to cancer. Whilst the current effort has been mainly focused on highly polluted environments, future research effort should be targeted at understanding the health effects of an exposure to a chronic low-to-medium oncogenic pollutant (or pollutant cocktail) level, also in combination with other ecological factors. In addition, often it is not the initial pollutant that is carcinogenic to an animal but a metabolised, or degraded version (eg. BaP). It is important to understand the processes around degradation of contaminants that could lead to increased mutagenesis in aquatic animals after their release into marine or freshwater environments (Smital et al., 2004). We recommend further studies focus also on how contaminants are transformed within aquatic environments to better understand the extent of carcinogenic pollution at every stage of its degradation.

Whilst there are several direct physiological links between pollutant exposure and oncogenic processes (such as oxidative stress and pollutant metabolism by-products), changes in pollution levels could also contribute to cancer development by more frequent occurrences of dysbiosis. One of the possible indirect pathways is a change in metabolism rate, which has been linked to cancer formation (Dang, 2012), and this trait also plays a significant role in processing xenobiotics (Sokolova and Lannig, 2008). Rapidly changing temperatures have shown evidence of altering the uptake and metabolism of benzo(a)pyrene, a known carcinogen, in gulf toadfish (*Opsanus beta*) (Kennedy & Walsh, 1994) which could potentially affect the likelihood of developing cancer. Another pathway includes the disruption of the microbiota

**Table 3**

Potential biomarkers of cancer that could be focused on in future research in the aim to develop non-lethal markers for cancer in aquatic species.

Biomarker	Link to cancer	Link to pollution	Species
Ahr (aryl hydrocarbon receptor)	AhR plays a role in autoimmunity, inflammation, resistance of cell death, evading growth suppressors, sustained proliferative signals and activation of invasion and metastasis (Kolluri, Jin & Safe, 2017) and can block key cancer hallmarks for various tumour types.	Can activate in response to PAHs and HAHs including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to detoxify xenobiotics (Zhang et al., 2015).	There is a wide range of AhR and its homologs found among metazoan species (Hahn, 2002).
Heat shock proteins	Induced by different stress signals and are often highly expressed in various cancers (Lianos et al., 2015). Evidence of anti-apoptotic properties. HSPs prevent the formation of nonspecific protein aggregates and assist in the acquisition of their normal architecture.	HSPs are known as biomarkers of physiological well-being and environmental health. HSPs are involved in protection and repair of cells following damage due to exposure to a variety of stressors including ultraviolet light, heavy metals and other contaminants (pesticides and PAHs) (Webb & Gagnon, 2009).	HSPs as a group are highly conserved chaperone proteins that are found among multiple eukaryote species groups as well as in prokaryotes as sHSPs (small heat shock proteins) (Kappé, Leunissen & de Jong, 2002).
microRNA	MicroRNA's often act as tumour suppressor molecules. Changes such as dysregulation of microRNA's, mutations that reduce microRNA binding efficiency and reduction of microRNA concentrations in tissues can increase cancer risk (Hayes, Peruzzi & Lawler, 2014).	Various chemicals are endocrine disrupting and cause increased upregulation of microRNA. Antifungals, dichlorodiphenyltrichloroethene, bisphenol A, fluoxetine (Cameron, Craig & Trudeau, 2016).	MicroRNA's play important regulatory roles across a wide range of multicellular organisms (Bartel, 2004).

balance that can impair gut microbiome function, causing metabolic and immune dysfunction and pathologies, including cancers (Scanlan et al., 2008; Meng et al., 2018).

Due to the combined impact of climate change and increasing pollution levels, system approaches might be necessary to evaluate, predict and to mitigate the effect of oncogenic processes in marine ecosystems. For example, mathematical modelling could aid the evaluation of individual/species sensitivity to cancer. These models could incorporate the combined effects of intrinsic and extrinsic factors, such as natural and life history of the species (migratory vs sedentary species, rank on food chain, genetic diversity etc.), metabolite variants, changing environmental conditions, dysbiosis etc., in order to identify species that may be at heightened risk of neoplasia development. Exploiting this already accumulated data from ecotoxicology research and combining it with “omics” approaches could be an efficient approach to discover potential early signs of cancer progression (Martyniuk & Simmons, 2016).

In conclusion, the synergistic and antagonistic interactions between pollution and other environmental stressors (e.g. warming water temperature and shortage in resource availability) could and may well increase species' sensitivity and susceptibility to oncogenic agents and oncogenesis. Without concerted efforts to develop non-lethal methods for detecting malignant transformations and understand the key variables in its formation, cancer may already be or might become a significant selective force in a much greater number of aquatic species than currently evidenced.

We hope that this article will make it easier for researchers studying this topic to get an overview of studies published so far, and thus be the starting point for many studies filling the current knowledge gaps in considering the role that cancer plays in health deterioration, physiological and life-history trade-offs, and mortality of species living in polluted aquatic environments.

#### 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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#### Appendix A. Supplementary material

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