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Impacts of endocrine disrupting chemicals on reproduction in wildlife and humans

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ABSTRACT

Endocrine disrupting chemicals (EDCs) are ubiquitous in aquatic and terrestrial environments. The main objective of this review was to summarize the current knowledge of the impacts of EDCs on reproductive success in wildlife and humans. The examples selected often include a retrospective assessment of the knowledge of reproductive impacts over time to discern how the effects of EDCs have changed over the last several decades. Collectively, the evidence summarized here within reinforce the concept that reproduction in wildlife and humans is negatively impacted by anthropogenic chemicals, with several altering endocrine system function. These observations of chemicals interfering with different aspects of the reproductive endocrine axis are particularly pronounced for aquatic species and are often corroborated by laboratory-based experiments (i.e. fish, amphibians, birds). Noteworthy, many of these same indicators are also observed in epidemiological studies in mammalian wildlife and humans. Given the vast array of reproductive strategies used by animals, it is perhaps not surprising that no single disrupted target is predictive of reproductive effects. Nevertheless, there are some general features of the endocrine control of reproduction, and in particular, the critical role that steroid hormones play in these processes that confer a high degree of susceptibility to environmental chemicals. New research is needed on the implications of chemical exposures during development and the potential for long-term reproductive effects. Future emphasis on field-based observations that can form the basis of more deliberate, extensive, and long-term population level studies to monitor contaminant effects, including adverse effects on the endocrine system, are key to addressing these knowledge gaps.

1. Introduction

Reproductive success in humans and wild animals is defined as an organism's capacity to produce offspring that will reproduce in the subsequent generation; thereby, ensuring an individual's genetic line. Measuring reproductive success in humans and domesticated species is relatively routine; however, for wild species this is challenging. Despite such challenges and the numerous factors influencing reproductive success in any given organism from natural abiotic (i.e., photoperiod, temperature, etc.) and biotic factors (e.g., parental, nutritional status, etc.), there is substantial evidence suggesting environmental chemicals decrease reproductive success in every major vertebrate taxa and in many invertebrate species (Fig. 1 and Tables 1 and 2). Many of these chemicals act by altering the function of the endocrine system components that mediate reproductive development. These chemicals belong to a group of chemicals called endocrine disrupting chemicals (EDCs). In Canada, an EDC is defined as a "substance having the ability to disrupt the synthesis, secretion, transport, binding, action, or elimination of natural hormones in an organism, or its progeny, that are responsible for the maintenance of homeostasis, reproduction, development or

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behaviour of the organism" (section 43 of the *Canadian Environmental Protection Act, 1999* (CEPA, 1999). Concern regarding the risks of EDCs to wildlife and humans is widespread, and global efforts to advance assessment methodologies are underway in several countries (Barton-Maclaren et al., 2022).

It is widely accepted that EDCs of anthropogenic origin are chemically diverse, ubiquitous in the environment (Metcalfe et al., 2021), and that exposure of wildlife and humans to multiple chemicals is occurring via food/water intake, inhalation, and direct contact. Legacy persistent organic pollutants (POPs) such as polychlorinated biphenyls (PCBs) have been reported in all environmental compartments globally (El-Shahawi et al., 2010), and many have continuing adverse effects on growth and reproduction (Bergman et al., 2015; Kortenkamp et al., 2011; Matthiessen et al., 2018). Anthropogenic chemical pollutants enter the environment through multiple routes. For example, alkylphenol ethoxylates, widely used for cleaning formulations and as industrial process aids, have been detected in municipal and industrial wastewaters, water from sewage treatment plants or landfill leachates (Acir and Guenther, 2018). PCBs and brominated flame retardants have also been reported in house dust, indoor, and outdoor air (Fan et al., 2014; Rudel and Perovich, 2009), and atmospheric transportation plays a major role in their global fate.

Complicating the risk assessment and regulation of EDCs is that levels of these chemicals in the environment vary over different time scales resulting in dynamic, multi-chemical exposure scenarios (Metcalfe et al., 2021). For humans, quantifying exposure to EDCs is relatively recent (i.e., over the last two decades), but is also revealing common widespread persistent exposure to a broad mixture of indoor and outdoor chemicals similar to those observed in wildlife (Chen et al., 2011; Gao and Kannan, 2020; Patandin et al., 1999; Rudel and Perovich, 2009). Ho et al. (this issue) reviews human exposure to EDCs in general human populations by describing the biomonitoring studies measuring chemical concentrations in blood, breast milk, urine, and adipose tissues. For example, current use chemicals such as parabens, bisphenols and phthalates have been detected in urine (van der Meer et al., 2021), halogenated flame retardants in adipose tissues and human milk (Pan et al., 2020), and legacy contaminants such as PCBs, dioxins, and furans in serum (Lambertino et al., 2021). Placental transfer has been demonstrated for various classes of EDCs (Mitro et al., 2015; Plante et al., 2021), confirming human exposure to these chemicals from the very early stages of life. Data on actual exposure are essential to define environmentally relevant concentrations for a broader range of EDCs in humans and wildlife alike.

Understanding the impacts of chemical exposures on reproductive success in wildlife and humans is a daunting task. It is complicated by diversity in reproductive strategies, varying knowledge of the endocrine control of reproductive development in different species and/or the ease at which reproductive success can be measured. As an example, human reproduction is well characterized, yet it is challenging to distinguish the impacts of EDCs amongst several confounding chemical co-exposures and lifestyle variables, due to the inability to perform experimental studies in humans to corroborate epidemiological findings and establish

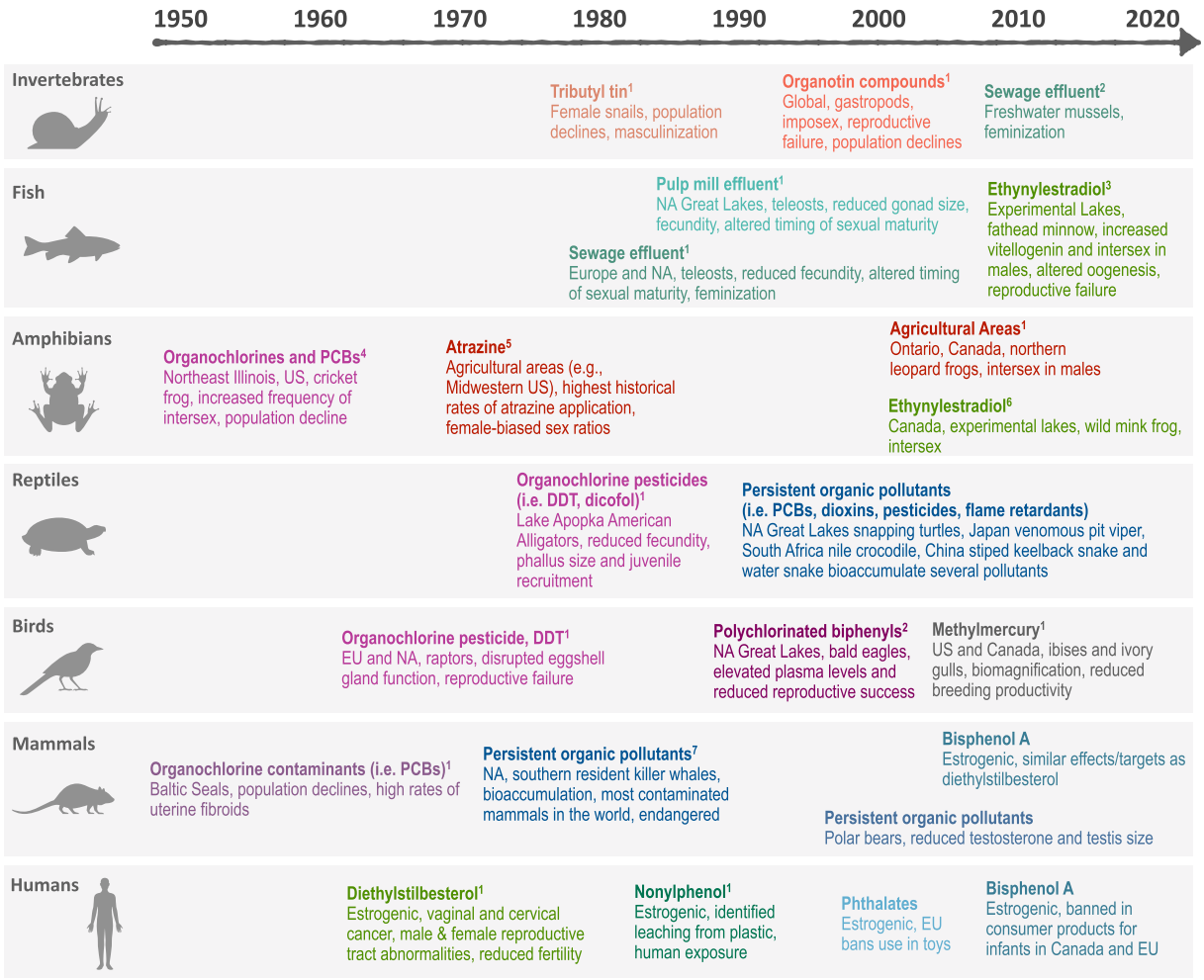

Fig. 1. Timeline of key examples of EDCs affec; ng reproduc; ve measures or bioaccumula; ng in wildlife and humans summarized in this review and/or in previously published reviews (indicated by numerical superscripts: 1. Bergman et al. (2012); 2, Matthiessen et al., 2018; 3. Kidd et al. (2007); 4, Reeder et al. (2005); 5, Van Der Kraak et al. (2014); 6, Park and Kidd (2005); 7, Lawson et al. (2020).

Table 1
Description of human male and female reproductive disorders for which EDCs exposure is a risk factor.

Fertility	Disorder	References
Fertility	Capacity to establish a clinical pregnancy.	Vander Borght and Wyns (2018).
Infertility	Failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse.	Vander Borght and Wyns (2018).
Decline in fertility	Increase of 0.37% and 0.29% per year in age-standardized prevalance of infertility for females and males, respectively, for the period from 1990 to 2017.	Sun et al. (2019).
	2009–2010 Canadian Community Health Survey: infertility prevalence range from 11.5% to 15.7%, significant increase compared with previous national estimates of 5.4% (in 1984) and 8.5% (in 1992).	Bushnik et al. (2012)
Miscarriage	Loss of pregnancy before viability. 23 million miscarriages per year worldwide; pooled risk of miscarriage of 15.3%.	Quenby et al. (2021).
Men	**Disorder**	**References**
Cryptorchidism	Non-descent of one or both testicles in the scrotum at birth.	Skakkebæk et al., 2015
Hypospadias	Congenital malformation of the penis where the opening of the urethra is in the underside of the penis instead of its tip.	Bergman et al. (2015); Skakkebæk et al., 2015.
Testicular cancer	2019 Canadian Cancer Statistics Annual Report: 1.3% yearly increase in its incidence between 1984 and 2015.	Purdue et al., 2005; Rosen et al. (2011); Gurney et al. (2019).
Decrease in sperm count and quality	Decline of 52.4% in sperm concentration between 1973 and 2001 in Western countries.	Levine et al. (2017); Sengupta et al. (2018).
Decrease in testosterone levels	Age-independent decline in total serum testosterone.	Travison et al. (2007).
Women	**Disorder**	**References**
Early menopause	Entry to menopause age 40–45 years old.	Faubion et al. (2015); Rossetti et al. (2017).
Primary ovarian insufficiency	Prior to age 40 cessation of ovarian activity. Oligo/amenorrhea (for at least 4 months). Evated serum follicle-stimulating hormone (FSH) levels (>25IU/l) on two occasions >4 weeks apart.	Nelson (2009); Vabre et al. (2017)
Polycystic ovarian syndrome	Oligo/anovulation, hyperandrogenism, polycystic ovarian morphology, as well as metabolic dysfunction. Increase of 1.45% from 2007 to 2017 in global age-standardized incidence rate.	Legro (2016); Liu et al. (2021).
Endometriosis	Ectopic endometrium (presence of endometrial glands and stroma outside the uterus).	Holoch and Lessey (2010); May et al. (2010); Zondervan et al. (2020); Plante et al. (2021)
Uterine fibroids	Benign tumors of the female reproductive tract. Cause of menorrhagia, pelvic pain, and pregnancy complications.	Grube et al. (2019); Kaganov and Ades (2016)

cause and effect relationships with EDCs. Nevertheless, for vertebrate taxa in general, there are several predominant neural and endocrine components conserved across species which regulate reproduction. In particular, the hypothalamic-pituitary-gonad (HPG) axis involves several neurohormones (i.e., sex steroids, gonadotropins, etc.) and signaling mechanisms (i.e., nuclear and membrane bound receptors, etc.) that regulate reproduction, in addition to other physiological processes (i.e., neuroplasticity, bone growth, metabolism, etc.). Many of these processes are targets of EDC actions. Invertebrates also possess neuroendocrine systems. The evolution of complex neuroendocrine systems occurred in several invertebrates including annelids, mollusks, insects, arachnids and crustaceans, and these systems are also targets of EDC actions (deFur, 2004). Although a full comparative review of the neural and endocrine controls of reproduction in vertebrates and invertebrates (reviewed in deFur, 2004 and IPCS, 2002) is beyond the scope of this critical review, several types of hormones (i.e. steroids, peptides, simple amides, and terpenes) and signaling mechanisms (nuclear and membrane bound receptors) comprise invertebrate neuroendocrine and reproductive systems. While a sound understanding of reproductive biology in the species under investigation is essential, a comparative reproductive approach to EDCs can yield valuable insights into mode of action and risks associated with chemical exposure.

The main objective of this review was to synthesize the current understanding of the impacts of EDCs on reproductive success in wildlife and humans by identifying adverse effects associated with, or known to lead to, reduced reproductive capacity in sexually mature individuals. For brevity, we focus exclusively on physiological and apical evidence from field-based investigations rather than molecular and laboratory-based studies. However, for some taxa epidemiological and/or field-based observations were scarce/non-existent and laboratory-based studies were presented as examples to maximize the survey of species included. To focus on how the impacts of EDCs may have changed over time, the examples selected often included a retrospective assessment of the knowledge of trends observed in Canada over the last decades. Despite the challenges associated with epidemiological and field-based studies, where possible we summarize the known molecular mechanisms of action and critical windows of exposure to EDCs leading to the observed adverse reproductive health outcomes in sexually mature individuals. Finally, where appropriate, gaps in knowledge were identified as these may limit our assessment of EDC effects on biota.

2. Effects of EDCs on reproduction

2.1. Invertebrates

Recent reports of the effects of EDCs on invertebrates have been increasing (Cuvillier-Hot and Lenoir, 2020). As invertebrates represent a significant proportion of worldwide biodiversity and perform crucial ecological roles in every ecosystem (Wilson, 1994) - with an estimation of more than 1,300,000 invertebrate species, comprising 97% of the living animals in the world (IUCN, 2014) - the study of the implications of EDCs on reproduction in invertebrates is of critical importance. Invertebrates are relatively small in size with high surface/volume ratios; thus, invertebrates are expected to be highly exposed to ambient contaminants, which can imply higher bioaccumulation (Cuvillier-Hot and Lenoir, 2020). However, few studies have addressed the reproductive consequences of EDCs on invertebrate species.

Two of the most well-documented examples of EDC effects on reproduction in invertebrates are the imposex and intersex phenotypes reported in species of *Mollusca* and *Arthropoda* (reviewed in Grilo and Rosa, 2017). Most of these phenotypical conditions are induced by organotin compounds such as tributyltin (TBT), triphenyltin (TPT), and dibutyltin (DBT) that are used as fungicides and pesticides on crops, as slimicides in industrial water systems, as wood preservatives, and as marine antifouling agents. Similar conditions were also reported following exposure to estrogenic compounds, such as 17β-estradiol and

17α-ethynylestradiol (Grilo and Rosa, 2017). The imposex phenotype is defined as non-functional male sexual organs that exclusively develop in females (Barroso et al., 2000; De Wolf et al., 2001). In contrast, the intersex condition encompasses individuals developing a gonadal tissue of the opposite sex (i.e., spermatocytes found in the ovary or oocytes observed in the testis (Bahamonde et al., 2013; Gomes et al., 2009). Both atypical phenological conditions are irreversible (Oehlmann et al., 1998) which leads to impaired reproduction, biased sex ratios, decreased fertility, and a risk for concomitant decline in species diversity and populations (Cuvillier-Hot and Lenoir, 2020).

The most definitive examples of the feminization of wild invertebrates in Canada are studies on the freshwater mussel *Elliptio complanata* living in the Saint-Lawrence River (Matthiessen et al., 2018). Studies conducted in 2003 reported that the number of female mussels caged in benthic pen cages downstream of a municipal effluent outfall significantly increased by 20% after one year of exposure compared with the upstream site (Blaise et al., 2003). Subsequently in 2007, individuals of *E. complanata* collected in two other locations near municipal effluent outflows in the St.-Lawrence River exhibited a dramatic increase in feminization downstream sites reaching up to 80% of the individuals, while the upstream sites yielded 30% which is within the expected range for this protandrous species (Gagné et al., 2011). Furthermore, the male *E. complanata* contained higher amounts of a female-specific vitellogenin-like protein levels. In addition, both the females and males living at downstream sites had reduced gonadosomatic indices compared to upstream *E. complanata* populations.

The molecular mechanisms mediating the effects of EDC-mediated imposex or intersex conditions in invertebrate species, are still unclear (Cuvillier-Hot and Lenoir, 2020; Grilo and Rosa, 2017; Katsiadaki, 2019; Langston, 2020). Currently, mechanistic data regarding intersex are derived from vertebrate literature, but given the vast evolutionary separation between these two groups, such interpretation is likely to be imprecise. However, like vertebrates, bivalves produce vitellogenin (VTG), the protein precursor of vitellin which is used as the primary nutritional source for the developing embryo, and recent studies suggest that it is also regulated by estrogen signaling as observed in oviparous vertebrate species (Tran et al., 2016; Zhu et al., 2018). VTG is a well-known biomarker for exposure to estrogenic chemicals in oviparous vertebrates. For example, a recent study reported the specific induction of VTG and VTG receptor gene expression in caged mussels (*E. complanata*) exposed for three months to municipal effluent discharge and to rainfall overflow sites in the St.-Lawrence River (André and Gagné, 2020). In concordance with these results, studies in Sydney rock oyster (*Saccostrea glomerata*) showed that exposure to 17β-estradiol increased VTG gene expression and this response was prevented using an estrogen receptor antagonist, suggesting estrogen receptors regulate VTG gene expression in oysters (Tran et al., 2016). Interestingly, others have reported lack of induction of VTG by 17β-estradiol in the marine bivalve *Mytilus edulus* (Puinean et al., 2006), highlighting potential species differences in VTG regulation and/or the need for further fundamental endocrinology research in this taxon. In addition, genes involved in gametogenesis (NASP, VTG, PCH2) increased in *E. complanata* at the contaminated St. Lawrence River sites along with genes involved in oxidative stress (superoxide dismutase, glutathione S-transferase) and DNA damage (chromosome mismatch and repair of covalently bound DNA adducts; André and Gagné, 2020). These studies demonstrate the endocrine-disrupting impacts of urban effluents on the reproductive endocrine axis in bivalves in addition to non-endocrine related impacts on DNA integrity and antioxidant capacity.

Both *D. magna* and *C. dubia* are commonly used crustacean models in chronic laboratory-based toxicity tests that include reproductive endpoints, such as the total number of offspring, offspring sex ratio, time to production of first brood, number and size of broods per organism, etc. (Tkaczyk et al., 2021). Offspring sex ratio is a key endpoint for EDCs in

Table 2
Summary of effects of EDCs on reproduction in field studies presented in this review across taxa with reference to example publications* describing these phenomena. Solid circles indicate effect observed and blank cell indicates not observed/not definitive evidence.

Effect	Invertebrates	Fish	Amphibians	Reptiles	Birds	Aquatic/semi-aquatic mammals	Humans
Molecular Level							
DNA damage or mutations	● [1]	● [5]					
Altered gonadal gene expression	● [3]	● [5]		● [11]		● [18]	
Altered sex steroid hormone levels	● [3]	● [5]		● [12]		● [19]	● [24]
Organ Level							
Gonadal masculinization/feminization	● [2]	● [5]	● [8,9]				
Gonadal abnormality	● [2,3]	● [5]	● [10]	● [11,12]	● [14,15]	● [20,21]	● [25]
Reproductive organ cancer						● [22]	● [26,27]
Organism Level							
Alterations of secondary sex characteristics		● [5]					
Alterations of Gametes		● [5]		● [12,13]			● [28]
Delayed sexual maturity		● [5]			● [16]		
Decreased fertility	● [4]	● [5,6]		● [12,13]	● [17]	● [23]	● [29]
Population Level							
Decreased offspring viability				● [17]	● [17]	● [22]	
Population declines	● [4]	● [5,6,7]	● [30]	● [17]	● [17]	● [23]	

* References for example studies pertaining to numbers above are provided in Supplementary Table 1.

Daphnia because it is controlled by juvenile hormones, thus it is possible to identify chemicals with juvenile hormone-like effects on crustaceans. Specifically, juvenile hormones play key roles in molting and maturation processes, and consequently, the shift of reproductive mode from parthenogenesis to sexual reproduction (i.e., production of male neonates; Tatarazako and Oda, 2007). Several chemicals have exhibited adverse effects on reproduction in *Daphnia* species, such as that observed with the antiepileptic pharmaceutical carbamazepine which caused a decrease in offspring number and increase in male offspring (Oropesa et al., 2016). Other examples include abnormal proportion of juveniles with nonylphenols, and BPA-mediated reductions in offspring production (Comber et al., 1993; Jeong et al., 2013, respectively). Data are lacking for effects of EDCs in wild populations of crustaceans and insects, but these advances in lab-based endocrine endpoints in *Daphnia* species could be adapted to field, micro- or mesocosm-based studies in freshwater and marine environments to better understand the ecological relevance of EDCs on these invertebrate populations.

2.2. Fish

Fish are probably the most extensively studied aquatic vertebrates and serve as a suitable model for studying the toxicological effects exerted by EDCs (Carnevali et al., 2018). Indeed, since the late 2000s, several fish laboratory-based bioassays to screen chemicals for toxic effects have been validated and standardized, including those screening for EDC effects mainly on the reproductive endocrine axis (reviewed in Robitaille et al., 2021). For these laboratory-based fish EDC screening toxicity tests with reproductive endocrine axis-related measures approximately a dozen species of the almost 30,000 existing teleosts are routinely studied, and most are small-bodied fish with relatively short life spans and reproductive cycles (e.g., fathead minnow, *Pimephales promelas*; zebrafish, *Danio rerio*). Despite this, several studies in wild fish populations corroborate EDC effects in laboratory-based toxicity tests. Collectively, reports of effects of EDCs on reproductive measures in wild fish species range from inhibition of gametogenesis, development of intersex gonads, alteration of the gonadosomatic index, altered sex steroids, decreased fertility and changes in epigenetic pathways inducing specific mechanisms of toxicity and/or aberrant cellular responses that may affect subsequent generation(s) through the germline (reviewed in Carnevali et al., 2018; Delbes et al., 2022). Furthermore, reports of the effects of EDCs on reproductive success in wild fish span continents, with some of the most well documented cases beginning in the 1990's downstream of sewage treatment plant and pulp mill effluent discharge pipes. Ultimately, based on numerous laboratory and field chemical/effluent exposure studies, the alterations to HPG axis reported in several wild fish are clear evidence that EDCs affect their reproductive fitness (Caldwell et al., 2008; Matthiessen et al., 2018; WHO/UNEP, 2016).

One of the earliest reports of intersex in fish associated with EDCs exposure was the study by Jobling et al. (1998) that linked high prevalence of gonadal intersex as well as changes in secondary sex characteristics in male roach (*Rutilus rutilus*) collected from rivers in the U.K. to discharges from sewage treatment plants. Subsequent follow-up studies showed that spermatogenesis was inhibited in male fish from these populations, while oogenesis in female fish was less affected compared to their male counterparts (Jobling et al., 2002). More recent studies in the Grand River watershed in Ontario, Canada, documented a high prevalence of intersex in males of two species of darters (*Etheostoma* sp.) collected downstream of wastewater treatment plants (Tetreault et al., 2011). Unlike the roach, darters spend their entire life history within a territory of a few square metres and thus, are reliable indicators of local exposure to EDCs. A key response also noted in the male darters to municipal effluent exposure was the induction VTG. Recent upgrades in sewage treatment within the watershed have resulted in reduced prevalence of intersex in the darters (Hicks et al., 2017). In other studies, upgrades of the wastewater treatment plant in Boulder Colorado, resulted in improved removal efficiency for many EDCs, particularly 17β-estradiol and estrone, and fathead minnow exposed to the post upgrade effluent showed reduced endocrine disruption relative to pre-upgrade conditions (Barber et al., 2012).

In another study, a whole lake study conducted at the Experimental Lakes Area in Canada involved the addition of low ng/L concentrations of 17α-ethynylestradiol to the lake over two field seasons. Data revealed that male fathead minnows (*Pimephales promelas*) developed intersex and other changes in testicular structure (Fig. 2). Notably, these investigations revealed rapid declines in the population of this fish species in the lake (Kidd et al., 2007). These studies provide strong evidence that exposures to estrogenic chemicals are linked to the development of gonadal intersex in male fish. The effects of estrogens on vitellogenin induction and the development of the intersex condition in wild fish populations are consistent with the results obtained in numerous studies in the laboratory (Gross-Sorokin et al., 2006; Santos et al., 2017). However, currently in Canada and in most countries, there are no mandatory EDC routine toxicity tests aimed at detecting EDC activity in sewage wastewater treatment plant effluents/receiving waters (Robitaille et al., 2021). As a result, there has been very little monitoring conducted to track the extent of impacts on aquatic wildlife, and no plan to advance to the tertiary treatment methods needed to substantially reduce the ongoing release of this point source mixture of pollutants.

Over the last 30 years, numerous studies conducted throughout the world have shown that effluents from some pulp and paper mills also affect fish reproduction (Hewitt et al., 2008; Munkittrick et al., 2003). This was first demonstrated in the Canadian context through field studies starting in the late 1980's in which white sucker (*Catastomus commersoni*) were collected downstream of a Bleached Kraft Mill at Jackfish Bay on Lake Superior. These fish exhibited altered reproductive development including reductions in gonad size, delayed sexual maturity, and reduced expression of secondary sexual characteristics (decreased nuptial tubercles in males) compared with fish collected at control sites (McMaster et al., 1996, 2006; Van Der Kraak et al., 1998). The altered reproductive responses in the white sucker were associated with effects on the endocrine signals mediating gonadal development. This included reductions in the levels of luteinizing hormone, reduced ovarian steroid biosynthetic capacity, reductions in the circulating levels of sex steroid hormones, and altered peripheral steroid hormone metabolism (Van Der Kraak et al., 1992). Noteworthy was the viability of eggs, sperm and developing larvae of these white suckers appeared to be normal (McMaster et al., 1992).

Since these initial reports, many additional studies soon followed.

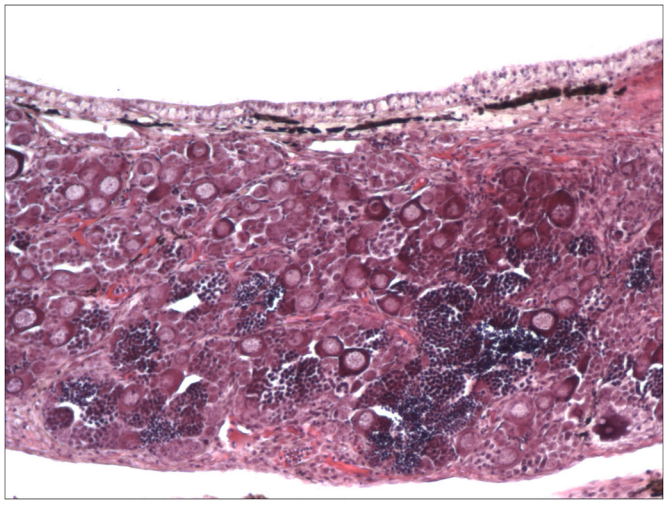

Fig. 2. Photomicrograph of an intersex gonad from a fathead minnow (*Pimephales promelus*) exposed to EE2 in Lake 260 by Karen Kidd and colleagues. Photo credit to Bob Evans of Fisheries and Oceans.

This included sampling of different wild fish populations in freshwater, marine and estuarine environments influenced by pulp and paper mill effluents and controlled laboratory exposures which examined the reproductive responses of fish resulting from acute and chronic exposures with adults to full lifecycle exposures starting with fertilized eggs. Consistently, these studies showed that many pulp and paper mill effluents contribute to altered reproductive responses (see Hewitt et al., 2008; Munkittrick et al., 2002). Controlled lab studies provided confirmation that the effluents were responsible for the observed effects. However, the compounds responsible for the reproductive effects seen in pulp mill-exposed fish have not been identified. Early studies demonstrated that phytosterols present in the effluents from a pulp mill in the United States were converted by bacteria to progesterone and then to androgens, which are thought to be responsible for the reproductive effects in fish (Jenkins et al., 2004). However, these compounds were not found at other sites nor were they present at sufficient concentrations to account for the effects on reproductive development (Hewitt et al., 2008). There is evidence that the effluents contain multiple ligands that are taken up and bind to sex steroid receptors and the aryl hydrocarbon receptor (Hewitt et al., 2000, 2003, 2005). This suggests that constituents present in the effluent function as EDCs and that there may be multiple pathways by which these chemicals affect fish.

In Canada, the discharge of pulp and paper mill effluents is regulated under the Fisheries Act. These regulations require Environmental Effects Monitoring (EEM) studies in the receiving waters to evaluate the effectiveness of the existing regulatory limits. A key component of the EEM program involves a comparison of wild fish populations at sites above and below effluent outfalls. Based upon initial EEM studies, a pattern emerged for fishes living in waters containing mill effluents; effluent-exposed fish populations were found to exhibit increased condition factors and larger livers, but smaller gonads (Lowell et al., 2005). This was interpreted as an indication of metabolic disruption with the potential to diminish overall reproductive capacity. Recently, the EEM program reported that effluents from 70% of pulp and paper mills are impacting fish and/or fish habitat (Environment and Climate Change Canada, 2019).

Given the challenges often encountered in collecting wild fish and concerns of overfishing, increased emphasis has been placed on using controlled laboratory exposures in determining the potential of pulp mill effluents to impact reproduction. Often this involves studies of effects on egg production in the fathead minnow following short-term (5 day) or medium-term (21 day) exposure to the effluent. These bioassays showed that effluents from 20 mills which use different processes (including Kraft, thermomechanical pulping, bleached chemi-thermomechanical pulping, recycled/paper/board, semichemical sulfite and dissolved sulfite) can negatively impact egg production (Kovacs et al., 2013; Martel et al., 2011, 2017). These effects on egg production were strongly linked to the organic content of the effluent, considered to be a measure of the efficiency of mill operating conditions. This led to recommendations related to mill process and function that would minimize the effects of pulp mill effluents on fish reproduction including i) controlling black liquor losses (including recovery processes and condensate handling), ii) consistently optimizing biological treatment systems, and iii) careful management of shutdown and start-up conditions. Environment and Climate Change Canada is proposing to implement limits on the release of effluent based on biochemical oxygen demand, chemical oxygen demand and the suspended solids (Environment and Climate Change Canada, 2019).

The Pulp and Paper industry in Canada has changed significantly over time. This has included installation and improvements to waste treatment systems, changes to the pulping process to reduce the potential for the formation of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F) through the substitution of chlorine dioxide (ClO_2) or other bleaching agents for elemental chlorine and in-plant measures for controlling the loss of organic chemicals related to mill operations. In the case of the mill at Jackfish Bay, changes to the operating conditions reflect installation of secondary waste treatment, changes in the pulp bleaching process, numerous facility maintenance shutdowns and a series of facility closures associated with changing ownership. Monitoring of the responses of white sucker to mill operating conditions has continued throughout all these changes over the past 30 years. The most recent studies show large improvements in hormone levels and increases in gonad and liver size in exposed fish (Bowron et al., 2009; Ussery et al., 2021). During the prespawning period, sex steroid levels in exposed fish were higher than in the past, but these remained more than 25% depressed relative to reference levels. There was also a dramatic improvement in the proportion of young fish in the spawning run, recovery of secondary sex characteristics, continued increases in fecundity and gonad sizes in prespawning male and female white sucker (Ussery et al., 2021). Thus, while reproductive impacts persist, it is apparent that improvements in mill operating conditions can lead to recovery of reproductive function in individuals.

2.3. Amphibians

Perturbation of the HPG axis in amphibians has been characterized through assessment of numerous endpoints, including sex ratios, gonadal differentiation, gametogenesis, gonadal morphology, reproductive behaviour, secondary sexual characteristics, hepatic vitellogenin circulating hormone levels and gene expression (reviewed by Orton and Tyler, 2015; reviewed by Trudeau et al., 2020). Moreover, a recent, multi-generational study in *X. laevis* demonstrated that EDC (50 ng/L benzo(a)pyrene) exposure reduced reproductive fitness in F2 progeny, which exhibited delayed sexual maturity, altered oocyte metabolome, and did not produce viable offspring (Usal et al., 2021). A significant body of literature from both field and laboratory studies has demonstrated that exposure to EDCs during critical developmental periods can disrupt gonadal differentiation, resulting in sex reversal (e.g., skewed sex ratios) and altered gonadal development (e.g., intersex).

Gonadal sex reversal is not easily evaluated in most amphibian species, as genetic markers of sex are not known, therefore, the proportion of male and female individuals compared to a control or reference population is used to approximate the frequency of sex-reversal. In several surveys of wild amphibians, skewed amphibian sex ratios have been observed in association with anthropogenic activity and hormonally active contaminants. Agricultural land use was recently associated with an increased frequency of female-to-male sex reversal in agile frogs (*Rana dalmatina)* in Hungary (Bókony et al., 2018; Nemesházi et al., 2020). Additionally, female-dominant sex ratios were documented in suburban and urban environments in Connecticut ponds contaminated with estrogenic EDCs (Lambert et al., 2015). Evidence of female-biased sex ratios following exposures to xenoestrogens has been intensively studied, with particular emphasis on the potent synthetic estrogen, 17α-ethynylestradiol (Tamschick et al., 2016). Exposure to 17α-ethynylestradiol at concentrations $\leq$5 nM has been associated a female-biased sex ratio in *X. laevis* (Villalpando and Merchant-Larios, 1990), *R. pipiens* (Hogan et al., 2008), and *S. tropicalis* (Pettersson et al., 2006). Moreover, in a whole-lake addition study in Ontario, Canada, 17α-ethynylestradiol (0.017 nM) caused a 28.2% increase in the frequency of intersex mink frog (*Rana septentrionalis) (*Park and Kidd, 2005). Similar effects on sex ratios have been observed for industrial contaminants (e.g., PCBs) and EDCs that effect sex steroid biosynthesis pathways (e.g., inhibitors of 5α-reductase (finasteride) and aromatase (fadrozole)) (Duarte-Guterman et al., 2009; Mackenzie et al., 2003; Olmstead et al., 2009).

To date, the majority of evidence implicates estrogenic and androgenic EDCs effect gonadal differentiation, and the majority of research on disruption of the amphibian reproductive axis has focused on pesticides. However, there is emerging evidence that other chemicals, sex steroids (e.g., progestogens; reviewed by Ziková et al., 2017) and regulators of other endocrine pathways (e.g., crosstalk with hypothalamus-pituitary-thyroid (HPT) axis; reviewed by Flood and

Langlois, 2014) are capable of inducing disruptions of reproduction in amphibians. Another class of agrochemical of emerging concern are steroidal growth promoters that are utilized in animal agriculture. Due to their inherent hormonal activity, pollution from these compounds raises concerns for non-target species. In North America, three natural steroids (17β-estradiol, testosterone, and progesterone) and their synthetic analogues (zeranol, trenbolone acetate, and melengestrol acetate) are authorized for use as growth promoters in beef cattle. Upon administration as either an implant or feed additive, a proportion of these veterinary drugs is excreted in urine or feces and subsequently may be transported to the aquatic environment through runoff (Khan and Lee, 2012; Lange et al., 2002). Emerging evidence suggests that such contaminants pose a threat as reproductive EDCs to amphibians, however, these concerns have not yet been well investigated. In particular, there is a lack of knowledge concerning the effects of progestogens (reviewed by Ziková et al., 2017) as well as the synthetic steroids zeranol, trenbolone acetate, and melengestrol acetate. While zeranol exhibits potent estrogenic activity, there is no information available on the reproductive effects of exposure in non-mammalian organisms. Trenbolone acetate was found to alter gonadal morphology and sexual differentiation in *X. laevis, Bufo viridis,* and *Hyla arborea* (Rozenblut-Kościsty et al., 2019), masculinize both *P. nigromaculatus* (Li et al., 2015) and *S. tropicalis* (Olmstead et al., 2012), in addition to accelerate Müllerian duct regression in *X. laevis* (Haselman et al., 2016). Finally, relatively little is known concerning the effects of melengestrol acetate on the amphibian HPG axis. Recently, a high concentration (1.7 μg/L) of melengestrol acetate, was found to alter gonad size and disrupt gene expression of sex-steroid and neuroendocrine genes in *S. tropicalis* tadpoles (Thomson et al., 2021; Thomson and Langlois, 2018). Considering their widespread use and presence in amphibian habitats in North America, future research should focus on characterizing the risk associated with these compounds on amphibian reproductive fitness.

2.4. Reptiles

In general data on the toxicity of chemicals to reptiles are sparse, and reptiles are currently not included as an *in vivo* or *in vitro* test species in any frameworks aimed at characterizing EDCs (Robitaille et al., 2021). Further complicating the understanding of the impacts of chemical exposure in reptiles is that they exhibit a wide range of life-histories, habitat preferences, reproductive and sex-determining mechanisms, and consequently the effects of EDCs on reptile reproductive status is undoubtedly different to some extent across reptile species. However, there is considerable conservation of several aspects of the HPG axis across vertebrates, including reptiles, and thus many of the population level, physiological and molecular indicators developed in other vertebrates to examine EDC effects have been employed successfully to study this phenomenon in reptiles.

One of the most extensive case studies of EDC effects on a reptile species is for the American alligator (*Alligator mississippiensis*) following an accidental spill of the pesticides dicofol and dichlorodiphenyltrichloroethane (DDT) into a tributary of Lake Apopka, Florida, USA in 1980. Lake Apopka also received extensive agricultural pesticide (mainly organochlorines) and nutrient runoff starting in the 1960's (Guillette et al., 2000). By 1983, Lake Apopka was declared an Environmental Protection Agency superfund site (i.e., area containing significant hazardous waste) and several studies performed by Guillette and collaborators reported significant development and reproductive impairment in alligators and other resident wildlife. Of great concern, during the 5 years following the pesticide spill, field studies revealed decreased clutch viability (i.e., number of eggs that hatch/number of eggs laid), increased juvenile mortality resulting in decreased juvenile recruitment (Woodward et al., 1993), a high incidence of hatchling and juvenile reproductive system abnormalities (i.e., altered sex steroid hormone profiles, reduced phallus size in males and abnormal ovarian morphology in females (Guillette et al., 1994)). These conclusions were drawn based on comparisons to other American alligator populations in less polluted lakes since no pre-spill field measurements on Lake Apopka alligators had been conducted (Masson, 1995; Woodward et al., 1993). More recent studies have shown that neonatal and juvenile alligators from Lake Apopka and a reference location, Lake Woodruff, exhibit differences in development, survival and a loss of sexually dimorphic and/or altered gonadal gene expression (i.e., steroidogenic factor 1, steroidogenic acute regulatory protein, cytochrome P45011A1, hydroxyl-delta-5-steroid dehydrogenase (Milnes and Guillette, 2008), activin subunits, follistatin and aromatase (Moore et al., 2010a, 2010b, 2010c, 2010b)). To date, there is strong evidence that Lake Apopka contaminants, mainly categorized as estrogenic persistent organochlorine-based pesticides, act via organizational effects causing abnormal gonadal morphology and function, and ultimately, population level declines in this American alligator population (Hamlin and Guillette, 2011). Furthermore, these results are generally supported by previous studies in wild crocodiles demonstrating exposure to anthropogenic pollution, including organochlorine pesticides, and reports of population declines (Ashton, 2010; Combrink et al., 2011; Rainwater et al., 2007; Wu et al., 2006), and in farmed Nile crocodiles (*Crocodylus niloticus*) whereby reduced clutch viability and HPG axis gene expression profiles (Arukwe et al., 2016) concur with many findings corresponding to those discerned from Lake Apopka alligators.

Studies of the effects of chemicals on reproduction in turtles are limited, but like alligators and crocodiles, several studies have demonstrated exposure to multiple chemicals with endocrine disrupting activity. Turtles are also long-lived high trophic level vertebrates, and it is not surprising that accumulation of POPs is reported in several species. Snapping turtles (*Chelydra serpentina)* in the Canadian or binational Great Lakes region are well-established indicators of localized environmental contamination of organochlorine pesticides, PCBs, PBDEs, inorganic compounds, sewage related contaminants and radionuclides as previously reviewed (Letcher et al., 2015). Furthermore, field studies on eggs and adult turtle plasma contaminant concentrations, hatching and deformity rates in several Areas of Concern in the Great Lakes region show higher concentrations of POPs that correlate to reduced reproductive success and development (de Solla et al., 2006, 2008; de Solla and Fernie, 2004; Letcher et al., 2015). In addition, detectable levels of various POPs have been reported in many of the seven species of migratory sea turtles (Camacho et al., 2012, 2013; Keller et al., 2004). Although no contaminant exposure experiments in sea turtles have been conducted in the laboratory due to their threatened or endangered status, Cocci et al. (2017) showed *in vitro* upregulation of estrogen receptor α transcripts in a dose–dependent manner in primary erythrocyte cultures after 48 h exposure to 4-nonylphenol and tri-m-cresyl phosphate. Collectively, despite a paucity of experimental cause and effect-based data in turtles, exposure and uptake of EDCs is evident, and it is hypothesized that impacts on the HPG is occurring, albeit to what extent is not known.

Although even fewer studies of lizards and snakes exist, there are reports of the impacts of environmental contaminants on various aspects of the reproductive endocrine axis in these Squamates using laboratory-based and field monitoring experimental designs. For example, the Mongolian racerunner (*Eremias argus)*, a small, oviparous Lacertid lizard endemic to eastern Asia (Kim et al., 2010) exhibited histological damage in the gonads and changes in gene expression after short-term oral exposure to several pesticides, including a pyrethroid insecticide (lambda-cyhalothrin; 7 day exposure to 10 mg/kg body weight; Chang et al., 2019), fungicide (prothioconazole; 100 mg/kg; 1 day exposure; Xie et al., 2019), and neonicotinoid insecticide (imidacloprid; 20 mg/kg body weight every 3 days for 28 days; Yang et al., 2020). Although none of these studies tested multiple concentrations of pesticides, the consistent adverse effects on gonad structure and gene expression changes in adult *E. argus* suggests potential for effects on reproduction especially during reproductive seasons for this oviparous lizard. Accumulation of contaminants in snakes was reviewed in Campbell and

Campbell (2001) and reported in several recent studies (Jones et al., 2009; Liu et al., 2018; Tashiro et al., 2021; Wu et al., 2020; Zhou et al., 2016) and these provide considerable evidence that EDCs (i.e., organochlorine pesticides, PBDEs, pharmaceuticals) are accumulating in several reptiles, each with the potential to impact different aspects of the reproductive endocrine axis. Furthermore, one dietary exposure to atrazine in gravid wild caught Northern watersnakes (*Nerodia sipedon;* viviparous and native to eastern and central North America) caused a male biased sex ratio (200 μg/kg) and decreased survival of offspring at birth (20 μg/kg; Neuman-Lee et al., 2014). Ultimately, in addition to the lack of toxicity studies or standardized laboratory or field-based toxicity testing methods for any of the ~9500 living reptile species that comprise the class Reptilia, the sensitivity of different reptile species to chemical contaminants, including EDCs is largely unknown.

2.5. Birds

Many natural and synthetic chemicals have been identified as EDCs of the avian HPG axis through laboratory testing and field studies (reviewed by Ottinger et al., 2011). Zebra finch (*Taeniopygia guttata*) are commonly used as a laboratory model for EDC assays (Adkins-Regan et al., 1990). Moreover, a framework for EDC screening has been developed in quail species (Northern bobwhite, *Colinus virginianus*; Japanese quail, *Coturnix japonica*) (Carere et al., 2010; Touart, 2004; US EPA, 1998). In the environment, birds may encounter EDCs through several routes of exposure including by maternal transfer, dietary, respiratory, or dermal exposures. Disruption of the HPG axis in birds can be characterized using endpoints related to reproductive behaviours, reproductive physiology, and reproductive success, ultimately contributing to effects on a population-level. Because of these sensitivities, avian-based biomarkers of endocrine disruption are valuable models for this field of toxicology.

As observed in other animals, impairment of endocrine signalling during sexual differentiation by EDCs in avian species can irreversibly alter the reproductive endocrine system structure and function (e.g., egg production, follicle development, testicular development, timing of sexual maturation), and reduce reproductive success. This is due to gonadal differentiation being dependent on appropriate sex steroid hormone levels during early stages of avian development. For example, embryonic exposure of Japanese quail to estrogens (e.g., diethylstilbestrol (DES), estradiol, ethynylestradiol, *o,p′*-DDT) causes feminization of sex organs and accessory structures in male chicks (Berg et al., 1999; Fry and Toone, 1981; Ottinger et al., 2008; Perrin et al., 1995; Rissman et al., 1984). In contrast, defeminization of the ovary and accessory structures in Japanese quail occurred following treatment with the anti-estrogenic compounds fadrozole or tamoxifen (Abinawanto et al., 1996; Elbrecht and Smith, 1992; Gildersleeve et al., 1985; Nishikimi et al., 2000; Perrin et al., 1995; Stoll et al., 1993). In field studies, gonadal morphology has been used to identify the presence of EDCs. For example, colonies of glaucous-winged gulls (*Larus glaucescens*) breeding in polluted areas of Puget Sound exhibited retention of the right oviduct in adult females, an indication of estrogen exposure (Fry et al., 1987; Rissman et al., 1984). The timing of sexual maturation is also relevant endpoint on a population scale, with potential, long-lasting effects on reproductive success. In several bird species, delayed sexual maturation has been observed following embryonic exposure to EDCs (e.g., PCBs, methoxychlor, genistein), likely through EDC-induced impairment of the GnRH-I system (Ottinger et al., 2001, 2009; Panzica et al., 2007). A multigenerational study found that sexual maturation was delayed in both male and female Japanese quail from eggs of hens exposed to methoxychlor (Ottinger et al., 2005).

A stark example of the adverse effects of EDCs in wild bird populations is evident in the case of reproductive failures due to eggshell thinning because of organochlorine pesticide contamination (reviewed in Bergman et al., 2012). Observations of impaired reproduction was documented in several species of fish-eating bird colonies in the Great Lakes (Gilbertson et al., 1991; Kubiak et al., 1989). Ratcliffe (1970) indicated that reproductive failure was associated with DDT contamination which caused eggshell thinning, rendering offspring unviable. Lundholm (1997) demonstrated that dichlorodiphenyldichloroethylene (DDE) acts by inhibiting prostaglandin synthase and reduces prostaglandin E2 in the eggshell gland mucosa, resulting in reduced calcium transport into the eggshell gland lumen and decreased eggshell thickness (Lundholm and Bartonek, 1992). After the introduction of control measures to limit the use and production of DDT, populations of many Great Lakes bird species, such as double-crested cormorants (*Phalacrocorax auritus*) and herring gulls (*Larus smithsonianus)* made dramatic recoveries compared to population sizes in the 1960s and 1970s (Giesy et al., 2003; Weseloh et al., 2002). Measured concentrations of DDT in bird tissues fell below levels known to cause eggshell thinning (Baumann and Michael Whittle, 1988; Giesy et al., 2003) and recently, a survey found that DDT levels measured in fish and air samples in the Great Lakes have been decreasing by a factor of two every 7–10 years (Hites and Holsen, 2019). This historical case is one of the most well-documented examples of endocrine disruption in wild bird populations as well as the success of conservation efforts.

While many fish-eating bird populations in the Great Lakes have recovered since regulations on the production and use of organochlorine pesticides in the 1970s, some North American bird species are once again facing concerning population declines (Hobson and Wilson, 2020; Nebel et al., 2010; Rosenberg et al., 2019). While the precise mechanisms remain unclear, evidence suggests that current pesticide use, particularly application of neonicotinoid insecticides as a seed coating, may be associated with reproductive impairments in birds and other non-target species. Recently, neonicotinoid use was shown to be statistically correlated with bird biodiversity loss in North America (Li et al., 2020), England (Lennon et al., 2019), and the Netherlands (Hallmann et al., 2014). Neonicotinoids were developed in the 1990s as replacements for environmentally harmful pesticides (e.g., organochlorines, organophosphates, and carbamates) (Schaafsma et al., 2015), and are currently the most widely used class of insecticide globally (Borsuah et al., 2020; Sultana et al., 2018). The high usage rate and dietary exposure pathway to birds (e.g., at high doses through consumption of pesticide-coated seeds) raises concern for the safety of neonicotinoids. The mechanism of neonicotinoid action as insecticides is by binding to the nicotinic acetylcholine receptor with higher affinity in invertebrates compared to vertebrates (Tomizawa and Casida, 2005). It is, therefore, plausible that neonicotinoid exposure may disrupt sexual behaviour by interfering with the neurotransmitter acetylcholine, which stimulates sexual arousal in vertebrates (Forlano and Bass, 2011; Mong et al., 2003). Moreover, thiacloprid, imidaclorprid (IMI), and metabolites of IMI have been shown to exert estrogenic activity (Kojima et al., 2004; Zhang et al., 2020). In addition to these mechanisms, neonicotinoids have been shown to perturb the HPG, HPT, and immune functions of several vertebrate species, including birds (reviewed in Gibbons et al., 2015; Leemans et al., 2019; Mesnage et al., 2018). For example, several studies have evaluated the effects of neonicotinoids in bird reproduction and demonstrated impairments on endpoints related to migration, fertilization success, egg size, eggshell thickness, embryo viability, hatching rate, and offspring survival (Eng et al., 2019; Pisa et al., 2017; reviewed by Gibbons et al., 2015). While the dataset on the effects of neonicotinoids on avian species reproductive success is incomplete, future studies are warranted to better understand their effects on bird populations.

2.6. Aquatic and semi-aquatic mammals

As many POPs with endocrine disrupting activity, such as PCBs, PBDEs, organochlorine pesticides (OCPs) readily bioaccumulate in lipid rich tissues, mammals can attain considerable body burdens. Further, due to biomagnification, their concentrations tend to increase with trophic position (Coppock and Dziwenka, 2017; Troisi et al., 2020).

Indeed, high concentrations of persistent EDCs at levels that may cause both reproductive and/or nonreproductive toxicities are detected in freshwater and marine mammalian species, such as mustelids, pinnipeds, odontocete cetaceans, and polar bears (Alonso et al., 2014; Dietz et al., 2018; Folland et al., 2016; Fossi and Marsili, 2003; Genov et al., 2019; Roos et al., 2012). Additionally, specific to these species is the fact that EDCs can cross the placenta and are excreted via colostrum and milk, thus part of the mother's body burden is transferred to the foetus and neonate *in utero* and during lactation, respectively, resulting in a high exposure of the developing young (Brown et al., 2016; Desforges et al., 2012; Herst et al., 2020). This perinatal exposure to EDCs, at a time when tissues are differentiating has been identified as a key window of sensitivity and a risk factor for long-term offspring health (Delbes et al., 2022; Diamanti-Kandarakis et al., 2009; Heindel and Vandenberg, 2015).

Some persistent chemicals like PCBs and other organochlorines are suspected to be responsible for population declines in minks and otters in Europe and North America (Basu et al., 2007; Elliott et al., 2018; Anna M. Roos et al., 2012; Wren, 1991). This can be attributed to their impact on male reproduction. For example, in adult American mink (*Neovison vison*), DDE concentrations have been shown to be negatively correlated with baculum (penile bone) length and weight (Elliott et al., 2018) and with the anogenital distance (AGD), a biomarker of "masculinization" during fetal development (Persson and Magnusson, 2015). Exposure to the emerging contaminants poly- and perfluoroalkyl substances (PFAS) which bio-magnify due to their proteinophilic characteristics and high resistance to biological degradation (Letcher et al., 2010), have been associated with lower AGD in males as well (Persson and Magnusson, 2015).

High levels of most organohalogen contaminants (OHCs) continue to be detected in apex predators, such as polar bears (*Ursus maritimus*), especially in "hotspots", such as Western and Southern Hudson Bay, Svalbard (Norway) and East Greenland (Gustavson et al., 2015a; Letcher et al., 2010). Exposure to OHCs has been associated with altered steroid and thyroid hormone levels, with PCBs suggested to exert the greatest influence on polar bear endocrinology (Ciesielski et al., 2017; Gabrielsen et al., 2015; Gustavson et al., 2015b). Size of polar bear baculum, testicles, ovaries were found to be inversely correlated to OHC concentrations (Sonne et al., 2006), potentially leading to altered reproductive success (Letcher et al., 2010). Furthermore, employing a risk quotient (RQ) analysis, Dietz et al. (2018) revealed that the additive RQs of OHCs in polar bears for reproductive, immune, and carcinogenicity/genotoxicity effects have been above the toxicity threshold for over three decades (Dietz et al., 2018). More importantly, in a meta-study of available data for 14 polar bear subpopulations, a negative correlation between population density and individual adipose tissue concentrations for ∑PCB, ∑DDT, ∑PBDE, and dieldrin was identified, suggesting that the observed individual negative health effects of these contaminants may extend to population-level consequences (Nuijten et al., 2016).

The Baltic grey seals (*Halichoerus grypus*) and ringed seals (*Phoca hispida*) are highly exposed to OHCs, and PCBs and DDT, in particular, have been implicated in uterine deformities and sterility, causing severe population size declines in these pinnipeds (Bernanke and Köhler, 2009; Fossi and Marsili, 2003; Harding et al., 2007; Roos et al., 2012). PCB contamination has been linked to the low rate of reproduction and population decline in Wadden Sea harbour seal (Phoca *vitulina*) as well (Reijnders, 1986). The causal effect being endocrine disruptive effects is strongly suggested due to the fact that PCB body burden was correlated with alteration of the expression of genes coding for the estrogen receptor α, thyroid receptor α and glucocorticoid receptor in young harbour seals (Noël et al., 2017) as well as with circulating concentrations of sex hormone levels in both, female and male adult ringed and grey seals (Troisi et al., 2020).

In cetaceans such as harbor porpoises (*Phocoena phocoena*), PCB body burdens have been associated with reduced testicular weight and elevated rates of reproductive failure (fetal death, abortion, and dystocia or stillbirth) (Murphy et al., 2015; Williams et al., 2021). Elevated levels of some PFASs are reported in Pacific humpback dolphins (*Sousa chinensis*) and bottlenose dolphins (*Tursiops truncates)* from the U.S. East Coast (Fair et al., 2012; Lam et al., 2016), and maternal-infant transfer, via placenta and milk, has been confirmed in several studies (Gebbink et al., 2016; Houde et al., 2006). Elevated PBDE levels were observed in beluga whales (*Delphinapterus leucas*) from the St. Lawrence Estuary and were 20–30 times higher than in beluga whales from the Canadian Arctic (Lebeuf et al., 2014). Based on examinations of stranded beluga carcasses between 1983 and 2012, in the St. Lawrence Estuary population, rates of dystocia (or delayed labour) and postpartum complications were the highest recorded in cetaceans worldwide. Infectious diseases were an important cause of mortality, particularly in juveniles, as well as malignant neoplasms, including mammary gland carcinomas found in 9.9% of females (Lair et al., 2016). Even if no causal link can be established between environmental contamination by EDCs and the health effects observed in beluga whales of the St. Lawrence Estuary, a statement can be made regarding contamination by POPs, including PCBs, DDT, HCH as well as PBDEs at much higher levels than in other beluga whale habitats (Lebeuf et al., 2014). Significant correlations between blubber concentrations of several POPs, as well as some emerging halogenated flame retardants (HFRs), and the transcription (in the skin) of genes involved in the regulation of thyroid hormones, gonadal steroids, and glucocorticoids have been observed in the St. Lawrence Estuary beluga whale population and in minke whales (*Balaenoptera acutorostrata)* visiting the region (Simond et al., 2019). By extrapolation with studies in other mammals, dystocia risk has been associated with nutritional stress and exposure to EDCs, such as PBDEs. Infections, also identified as a leading cause of death in belugas of all ages, are associated with immunosuppression due to exposure to chemical contaminants including PCBs. Finally, neoplastic effects on mammary glands are associated with estrogenic effects of organochlorine compounds including PAHs from aluminum smelters that once contaminated the environment (Lair et al., 2016).

2.7. Humans

About 16% of heterosexual couples of reproductive age experience infertility, an incidence that has almost doubled between 1992 and 2012. Consequently, infertility has been identified as a priority for the medical research community, for service providers, and for policy makers (Quenby et al., 2021). This trend can be attributed to changes in lifestyle, diet, reproducing at older ages and to exposure to environmental pollutants such as EDCs. Epidemiological evidence of EDCs affecting human reproduction are detailed in Table 1 and below for both men and women.

2.7.1. Men

The reproductive health of men living in developed countries is declining (Levine et al., 2017; Niels E. Skakkebæk et al., 2015; Swan and Colino, 2021). Epidemiological studies suggest that there has been an increase in the incidence of male reproductive disorders for more than 50 years. These disorders summarized in Table 1 include cryptorchidism, hypospadias, testicular cancer, a decrease in circulating testosterone levels, and a decrease in the number and quality of spermatozoa. In 2001, Skakkebaek and colleagues hypothesized that these pathologies were symptoms of a single syndrome with a common fetal origin that they named the testicular dysgenesis syndrome (TDS), which has a fetal origin (Skakkebæk et al., 2001, 2015). Since then, epidemiological evidence has shown that the four symptoms of TDS are interconnected in a network of risk factors, i.e. the occurrence of one of the pathologies represents a risk factor that may lead to the appearance of one or more other symptoms of TDS. Interestingly, the occurrence of one or more TDS pathologies is also associated with the feminization of AGD (Schwartz et al., 2019; Swan, 2006; Swan et al., 2005). In humans, AGD

is the distance from the center of the anus to the genitalia (Fischer et al., 2020). This distance is normally 1.5 to 2 times longer in males than in females and is used as a biomarker of androgen action during fetal development (Schwartz et al., 2019). Several studies have shown that males with cryptorchidism, hypospadias, low sperm count or low androgen levels have a short AGD (Eisenberg et al., 2011, 2012; Swan, 2006; Swan et al., 2005; Thankamony et al., 2014). Various factors may be responsible for the increase in these abnormalities, including *in utero* exposure to EDCs exhibiting estrogenic or anti-androgenic activity that interfere with the endocrine system of the developing organism (Delbes et al., 2022).

Exposure of pregnant women to the synthetic estrogen DES is a telling example of the adverse effects of *in utero* exposure to an endocrine disruptor on the reproductive health of the offspring (Ho et al., 2022; Delbes et al., 2022). Follow-up of childhood cohorts showed that exposed boys had a higher risk of cryptorchidism (Gill et al., 1979; Palmer et al., 2009), hypospadias (Brouwers et al., 2006; Klip et al., 2002; Palmer et al., 2009; Toppari et al., 2001) and low sperm count in adulthood (Gill et al., 1979; Leary et al., 1984). Another estrogenic compound studied in association with TDS in humans is BPA for which a negative correlation has been shown between its level in cord blood and the level of expression of the hormone Insulin-like 3 (INSL3) in boys with cryptorchidism (Chevalier et al., 2015). Also, a dose-dependent association between short AGD has been shown in boys whose mothers were exposed to BPA during pregnancy via their occupation (factories employees exposed to BPA) (Miao et al., 2011). Finally, exposure to BPA in adulthood has been associated with decreased sperm concentration in humans (Li et al., 2011; Meeker et al., 2010).

Many studies suggest an association between exposure to phthalates and hormonal disruption resulting in incomplete virilization (undermasculinization) of boys exposed *in utero* (Main et al., 2006; Matsumoto et al., 2008; Swan et al., 2005). For example, Main and colleagues found an association between the levels of monomethyl phthalate, mono-ethyl phthalate and mono-n-butyl phthalate in breast milk and the free LH: testosterone ratio in 3-year-old boys suggesting an alteration in testicular function during breastfeeding, however without incidence of cryptorchidism (Main et al., 2006). In another Danish study, high levels of phthalate metabolites and diisononyl phthalate (DiNP) in amniotic fluid were correlated with high odds ratios for cryptorchidism and hypospadias, but without association with steroid hormone or INSL3 levels in amniotic fluid (Jensen et al., 2015). At the same time, an inverse association has been demonstrated between AGD, penile width and maternal urine phthalate levels in the 1st and 2nd trimesters of pregnancy but not in the 3rd trimester (Jensen et al., 2016; Martino-Andrade et al., 2016). This is consistent with the adverse effects of hormonal disruption during the masculinization window, which is defined between gestational week (GW) 8 and 14 in humans (reviewed in Delbes et al., 2022). In longer term, it was shown that the presence of di (2-ethylhexyl) phthalate (DEHP) and DiNP metabolites in maternal serum is negatively associated with low testicular volume and low sperm volume (Axelsson et al., 2015). The concentration of monoethyl phthalate and mono-carboxy-isooctyl phthalate in maternal serum (collected between SG18 and SG34) has been negatively associated with sperm volume and sperm motility of sons in adulthood respectively (Hart et al., 2018). Very recently, maternal occupational exposure to phthalates has been correlated with low semen volume and total sperm count in their sons (Istvan et al., 2021).

Other anti-androgenic chemicals have been associated with TDS. This is the case of organochlorine pesticides such as DDE, PCBs, hexachlorobenzene, chlorodanes or DDT linked to risk of developing testicular cancer (Cohn et al., 2010; Giannandrea et al., 2011; Hardell et al., 2003; McGlynn et al., 2008). Small but significant higher risk of hypospadias in boys whose mothers were exposed to pesticides during pregnancy was also shown in a meta-analysis (Rocheleau et al., 2009). Three studies in France, Denmark and Finland showed an association between the level of pesticides in breast milk and colostrum and boys' risk of cryptorchidism (Andersen et al., 2008; Brucker-Davis et al., 2008; Damgaard et al., 2006). A very recent study showed long term effect of maternal occupational exposure to pesticides on low semen volume and total sperm count in their sons (Istvan et al., 2021). Finally, there is considerable evidence that adult exposure to pesticides has adverse effects on male fertility by reducing sperm count and inducing azoospermia (reviewed in Goldsmith et al., 1984; Martenies and Perry, 2013; Potashnik et al., 1978; Whorton et al., 1979).

Other chemical compounds have been implicated in TDS through endocrine disruption. These include flame retardants that have been associated with hypospadias (Carmichael et al., 2003), cryptorchidism (Goodyer et al., 2017; Main et al., 2006) and testicular cancer (Hardell et al., 2006); heavy metals that have recently been associated with long term negative impact on semen volume and sperm count after *in utero* exposure (Istvan et al., 2021), and analgesics such as acetaminophen and ibuprofen that have been shown to alter human fetal gonad development, although the available data are still controversial (reviewed in Zafeiri et al., 2021). Together these epidemiological data support the fetal origin of TDS due to exposures to EDCs during key developmental phases having long-term consequences on reproductive success, as well as adult exposure causing adverse reproductive outcomes.

2.7.2. Women

In contrast to apparent male reproductive health decline, global trends in female reproductive disorders (defined in Table 1) are more difficult to establish, partly due to constantly evolving diagnostic criteria (Amato et al., 2008) and the lack of reliable non-invasive diagnostic tools (Ghiasi et al., 2020a; Zondervan et al., 2020). Nevertheless, considerable prevalence for numerous reproductive pathologies, affecting women's ability to conceive and overall birth rates is reported recently.

Female reproductive lifespan is largely determined by the size and the quality of the primordial follicle pool established early in life (the ovarian reserve) (Jirge, 2016). A dynamic decline in this pool occurs within the human ovary with age, culminating in the natural menopause at age 50 ± 4 years (Depmann et al., 2015). However, it has been estimated that large numbers of women worldwide are suffering from early menopause (EM) or will experience primary ovarian insufficiency (POI), 12.2% and 3.7% respectively (Golezar et al., 2019). Furthermore, certain maternal and environmental factors can disrupt oogenesis contributing to compromised oocyte quality and leading to arrested development, reduced fertility (see Table 1), and epigenetic defects that affect offspring long-term health (Delbes et al., 2022; Mtango et al., 2008; Plante et al., 2021). An increase of 1.45% from 2007 to 2017 in global age-standardized incidence rate for polycystic ovarian syndrome (PCOS) (Liu et al., 2021) was reported, which affects between 5% and 20% of women of reproductive age (Azziz et al., 2016). Furthermore, ovulation disorders like PCOS and POI, are estimated to account for infertility in about 1 of 4 infertile couples (Duursen et al., 2020). Endometriosis and uterine fibroids (UFs), often present as comorbidities in diseased patients, are further contributing to women's infertility (Uimari et al., 2011). Found in up to 80–90% of women at the age of 50 (Grube et al., 2019; Parker, 2007), UF are associated with increased risk of pregnancy loss and obstetric complications and may be the sole cause of infertility in 2–3% of women (Freytag et al., 2021). Endometriosis prevalence at the population level ranges between 0.7% and 8.6%, yet among infertile woman is up to 68% (Eisenberg et al., 2018; Ghiasi et al., 2020b). This pathology is further associated with decreased oocyte quality (Xu et al., 2015) and increased risk for reproductive-site cancers (Kvaskoff et al., 2014; Zondervan et al., 2020).

A growing body of evidence in the last few decades implicates EDCs in the aetiology of reproductive pathologies (Diamanti-Kandarakis et al., 2009). Precise endocrine signalling is involved in all aspects of the development and functioning of the female reproductive system. Indeed, despite their multifactorial nature, estrogens seem to play a central role in disease pathogenesis of endometriosis and UFs (Borahay et al., 2017;

Upson, 2020). In addition, overexposure to androgens *in utero* is thought to be responsible for PCOS development later in life (Filippou and Homburg, 2017) and can also affect among others, the early establishment of ovarian reserve (Johansson et al., 2020; Richardson et al., 2014). Therefore, the extreme sensitivity of the female reproductive system to disruption by chemicals that may interfere with estrogen and androgen synthesis and actions, together with the timing of the exposure are important considerations for the later outcome (Fowler et al., 2012). Similar to male TDS, ovarian dysgenesis syndrome (ODS) hypothesis proposes that some adult female reproductive health problems, such as reduced fertility, PCOS, POI, endometriosis and reproductive-site cancers, might have a common origin and result from early alterations of ovarian structure or function related to *in utero* chemical exposure, including EDCs (Delbes et al., 2022; Johansson et al., 2017, 2020). Further, these effects may be triggered or worsened by EDCs exposure throughout a woman's life (Johansson et al., 2020). The most well-known example linking human fetal EDCs exposures with adult-onset reproductive disorders is provided by DES. Indeed, *in utero* DES exposure in females is associated with increased risk for development of clear cell adenocarcinoma (CCA) of the vagina and cervix, higher rates of genital tract abnormalities and adverse pregnancy outcomes (al Jishi and Sergi, 2017; Veurink et al., 2005), diagnosis of endometriosis, UFs and EM (Baird and Newbold, 2005; Hatch et al., 2006; Missmer et al., 2004). Human studies on prenatal exposure to EDCs and female reproductive disorders are still a major data gap, nevertheless higher levels of chemicals, particularly those associated with plastics and food packaging, are found in many diseased patients compared to control subjects. For example, BPA is thought to affect the ovarian reserve, as higher urinary BPA levels were inversely associated with antral follicle count (AFC) (Czubacka et al., 2021; Souter et al., 2013) and, number of retrieved oocytes and number of normally fertilized oocytes in *in vitro* fertilization cycles in women undergoing medically assisted reproduction (MAR) (Ehrlich et al., 2012; Mok-Lin et al., 2010). Further, maternal serum BPA levels early in pregnancy were associated with a higher risk of aneuploid and euploid miscarriage (Lathi et al., 2014). Higher BPA levels were reported in women with PCOS compared to controls (Hu et al., 2018), however, human evidence linking endometriosis risk with BPA exposure is inconsistent (Peinado et al., 2020; Rashidi et al., 2017; Simonelli et al., 2017). As for phthalates, higher urinary concentrations of some phthalate metabolites were associated with significant decrease in AFC (Messerlian et al., 2016), as well as reduced oocyte yield, fertilized oocytes, and top-quality embryos (Hauser et al., 2016; Machtinger et al., 2018) in women undergoing MAR. Further, higher monoethyl phthalate levels in maternal serum during pregnancy were associated with reduced serum anti-müllerian hormone (AMH) levels (a marker of ovarian reserve) in their adolescent daughters (Hart et al., 2014). Phthalate exposure is associated with lower odds of having PCOS in most studies (Akgül et al., 2019; Hart et al., 2014; Vagi et al., 2014). Overall positive correlations were reported between plasma concentrations of phthalate esters and endometriosis diagnosis, in particular for di-n-butyl phthalate (DnBP), butyl benzyl phthalate (BBzP), DEHP and di-n-octyl phthalate (DnOP; Cobellis et al., 2003; Kim et al., 2011; Reddy et al., 2006a, 2006b), as well as with urinary phthalate metabolites (Buck Louis et al., 2013; Cai et al., 2019; Kim et al., 2015). Evidence for phthalate exposure association with the risk of UFs is inconsistent (Kim et al., 2016; Pollack et al., 2015; Sun et al., 2016; Weuve et al., 2010). These correlations in women between both BPA and phthalates and effects on the ovaries and uterus are well supported by numerous *in vivo* and *in vitro* animal studies demonstrating these compounds have estrogenic modes of action (Delbes et al., 2022; Cheon, 2020; Tomza-Marciniak et al., 2018). Many other EDCs identified in experimental animal studies from various chemical categories have also been suspected to affect female reproductive system. Detection of PFAS in follicular fluid in woman undergoing MAR was associated with lower fertilization rate and number of embryos transferred (Governini et al., 2011). Higher serum concentrations for certain PFAS have been associated with increased risk for EM (Knox et al., 2011; Taylor et al., 2014) and were reported in PCOS (Vagi et al., 2014) and endometriosis patients (Campbell et al., 2016a). Pyrethroid pesticide exposure has been suspected to play a role in POI (Li et al., 2018). Exposure to organochlorine chemicals, including PCBs, OCP and dioxins has been associated with endometriosis diagnosis (Cano-Sancho et al., 2019), as well as with increased risk for EM (Akkina et al., 2004; Eskenazi et al., 2005; Grindler et al., 2015) and POI (Pan et al., 2019). PCBs and DDE exposure has been associated with PCOS (Yang et al., 2015) and UFs development (Trabert et al., 2015).

In conclusion, based on the epidemiological evidence and supporting non-human studies for several suspect or known EDCs, chemical exposure is undoubtedly affecting women's reproductive health. However, the precise EDC thresholds, mechanisms, and extent for most chemicals in commerce requires further inquiry.

3. Common indicators and EDCs affecting reproduction

Although the data outlined in this review demonstrate the effects of EDCs on the reproductive endocrine axis vary somewhat in all taxa, several endpoints and EDCs are common to vertebrate and even invertebrate species (Table 2). For example, estrogenic EDCs such as organochlorine pesticides and sewage effluents are strongly associated with observations of direct effects on the ovaries and testes as indicated by gonad abnormalities in all taxa (Table 2). These observations of chemicals interfering with some aspects of the reproductive endocrine axis are particularly pronounced for aquatic species and are often corroborated by laboratory-based data sets (i.e. fish, amphibians, birds), and many of these same indicators are also observed in epidemiological studies in mammals. For example, positive correlations between many of these same EDCs (i.e., DDT, BPA, phthalates) to effects on ovarian and testicular structure and function in wild mammals and humans are evident. The DES case study whereby administration to pregnant women *in utero* leading to offspring with gonadal abnormalities (structural and functional) and cancers in both males and females provides further evidence of the potent effects of estrogenic chemicals during human development. Based on the studies in lower vertebrates linking molecular, organ and organismal level impacts of EDCs to reproductive success (i.e., organochlorine pesticides, organotin compounds, sewage, and pulp mill effluent effluents), it is likely that EDCs are contributing to reduced reproductive success in mammalian wildlife and humans despite the lack of controlled experimental studies to support epidemiological findings in these higher vertebrates.

Ultimately, some of the most common EDCs (i.e., DDT, BPA, phthalates) bind to and inhibit or activate estrogen or androgen receptors in multiple vertebrate species. This is no doubt, in part, due to the focus on detecting estrogenic and androgenic mechanisms of action in controlled experimental and field studies and the lack of methods to detect other mechanisms of endocrine action until recently (reviewed in Robitaille et al., 2021). Nonetheless, the evidence to date continues to corroborate the notion that EDCs identified as sex steroid agonists or antagonists have high potential for inducing a molecular initiating event leading to adverse reproductive outcomes in wildlife and humans. With steroids and their receptors widely dispersed throughout vertebrates and sex steroid-like receptors recently discovered in some invertebrates, it is not surprising that EDCs exerting their actions via sex steroid receptor interactions elicit adverse effects on reproduction in multiple vertebrate and invertebrate taxa. Consequently, it is clear that the sex steroid receptor screening assays reviewed and recommended as predictive, high-throughput tools for identifying chemicals with high potential for adverse impacts on reproduction by Robitaille et al. (2021) and Barton-Maclaren et al. (2022) are supported. Undoubtedly high throughput cell-based assays will aid in identifying those chemicals of high concern as reproductive EDCs, which can then be prioritized for subsequent investigations in the natural environment.

Despite the advances in our understanding of the ecological

relevance of EDC mechanisms of action in recent years, long-term, continuous field studies complimented with controlled experimental studies are still needed to fully assess the impacts of EDCs at the population level in representative wildlife. Indeed, few field studies are long enough in duration to capture the full reproductive life cycle in vertebrate wildlife, let alone multiple generations to understand natural baseline or contaminant induced changes. Ideally, field surveys over multiple generations monitoring population levels, reproductive and non-reproductive health measures in more wildlife species integrated with *in situ* exposures and/or mesocosms as well as controlled laboratory experiments are recommended to establish cause and effect. Fig. 1 and Table 2 highlights several species and examples of field-based observations that can form the basis of more deliberate, extensive and long-term population level field studies to monitor contaminant effects, including adverse effects on the endocrine system. For example, the EEM Program in Canada includes standardized, long-term monitoring and effect thresholds for fish and benthic invertebrate populations to monitor the impacts of pulp and paper mill effluents, including some reproductive endpoints in fish. This program could be applied to monitor sewage effluent effects in fish and invertebrates or other contaminated waters, and enhanced with additional reproductive system endpoints (i.e., vitellogenin, hormone levels, gonad histopathology). This integrative approach would provide the evidence needed to assess the risk of the low-level, multi-EDC exposure scenarios wildlife are experiencing, track recoveries after efforts to remediate and work towards establishing adverse outcome pathways that can be translated into *in vitro/in silico* screening and modelling methodologies. Lastly, fundamental studies on reproductive endocrinology are lacking for most wild animals but are particularly sparse for most invertebrates, non-crocodilian reptiles and top predators, indicating critical knowledge gaps that need to be addressed and considered when selecting sentinel wildlife for ecotoxicological investigations.

Similarly, there is great need to better monitor human exposure levels to EDCs and establish how this contributes to the increasing incidences of disorders of the reproductive tract and declining fertility rate in both women and men. There is now evidence of sensitive timing of exposure, more specifically during development, which underlines the importance of identifying populations at risk from a biological point of view (i.e., pregnant women and the foetus, newborn) but also possibly in relation to socio-economic status (i.e., occupational and residential exposures). Follow-up cohorts exist in Canada to monitor mother-child health (CaMCCo Canadian Mother-Child Cohort); however, specific monitoring of the issue of EDC exposure on long-term reproductive health over one or more generations requires further investment and support. Environmental health is becoming a topic of interest to the general public, thus, there is a need to better understand the physiology of reproduction and the mechanisms by which EDCs act. This is imperative to not only find ways to counteract their negative effects, but also to better inform and educate young people and people of reproductive age of the possible effects.

4. General conclusions

The studies summarized within this publication reinforce the concept that reproduction in wildlife and humans can be significantly impacted negatively by human-made chemicals, many of which act by altering the function of the endocrine system. Given the vast array of reproductive strategies used by animals, it is perhaps not surprising that no single endpoint is predictive of reproductive effects. There are some general features of the endocrine control of reproduction and in particular the critical role that steroid hormones play in these processes that confer a high degree of susceptibility to environmental chemicals. The ability of environmental chemicals to interact with estrogen and androgen receptors renders these pathways particularly sensitive to chemical insults. Other ligand activated receptors including progesterone, retinoid and aryl hydrocarbon receptors represent molecular targets that are uniquely sensitive to disruption by environmental chemicals. Further work on characterizing the role that these types of receptors play as initiators of the molecular pathways controlling reproduction will add more clarity in understanding how chemical disturbances can cause reduced reproduction. Steroid hormones function as both activational and organizational regulators of cells, and ultimately, whole animal function which makes the timing of exposure so critical to understanding how they impact development. The organizational events are often permanent in nature and as such move animals on an irreversible path of development. Much more work is required to understand not only the thresholds for effects on development, but to discern the implications of developmental period exposure. Furthermore, EDC research should overcome the "silo research straightjacket" as clearly human health science and wildlife science can beneficiate from each other's findings.

Studies over the last 50 years have shown that many different classes of chemicals can function as EDCs. It is not just legacy compounds that can effect reproductive function, but many pharmaceuticals and new compounds added to the marketplace (e.g. PFAS, neonicotinoid insecticides) act as EDCs. Recently much effort has been placed on the development of replacement chemicals for known EDCs such as BPA and perfluorinated compounds. Unfortunately, many of these replacement compounds function as EDCs (Berni et al., 2019b; Cui et al., 2020b; Eladak et al., 2015b; Ikhlas and Ahmad, 2020b; Luo et al., 2021b), and thus, do not generally offer a greater degree of safety. Perhaps the ultimate factor in reducing the risks posed by EDCs will be to reduce exposure, and this might be achieved through improved public awareness and vigilant product stewardship by both manufacturers and consumers.

Credit author statement

All authors contributed to the planning and writing of the manuscript. VLM was the lead in planning the manuscript and is the corresponding author. All other authors are listed in alphabetical order.

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 data

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