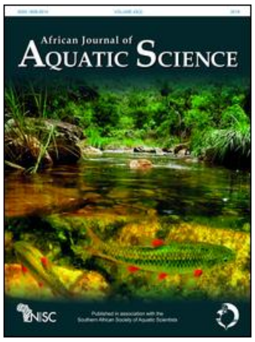

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*Review article*

# Threats posed by xenoestrogenic chemicals to the aquatic ecosystem, fish reproduction and humans: a review

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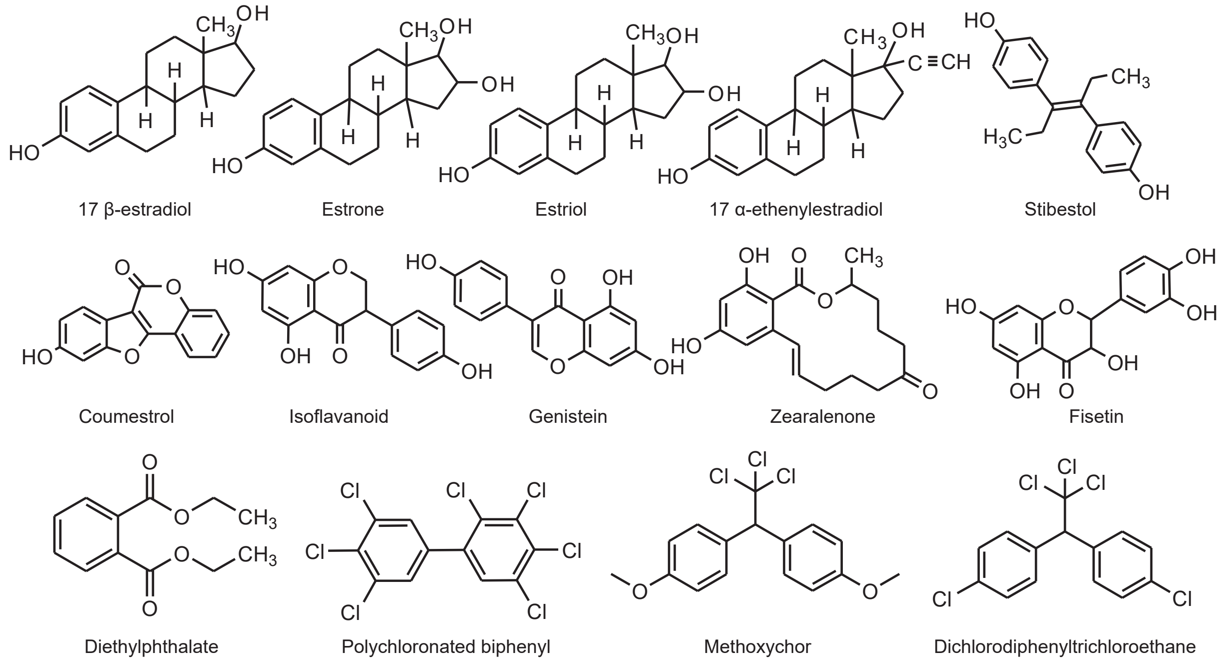
**Xenoestrogens mimic and interfere with natural functions of oestrogens and adversely affect fish reproduction. Pesticides, plastics, wastewaters and pharmaceuticals are sources of xenoestrogens, and are carried through surface runoffs to water bodies at concentration levels that are harmful to aquatic organisms. Fish absorb xenoestrogens through ingestion of contaminated food items, respiratory gills and dermal contact. Xenoestrogens bioaccumulate in fish tissues, eliciting various reproductive abnormalities, e.g. males may abnormally produce vitellogenins and present with reduced sperm counts, whereas females experience reduced fecundity and hatchability of eggs. Through the food web, xenoestrogens biomagnify in fish predators, e.g. seals and humans, which in turn risk suffering from reproductive malfunctions. Studies of adverse impact of xenoestrogens on fish have mainly been limited to developed countries, yet fish are a major food and trade commodity for developing sub-Saharan African countries. This review serves as a basis for research on adverse impacts of xenoestrogens on fish reproduction, and other consumers of aquatic organisms in Lake Victoria. The lake receives high levels of pollutants from untreated or poorly-treated domestic and industrial wastes and agro-chemicals. Control of xenoestrogens requires concerted effort from multistakeholders to undertake activities such as surveillance, advocacy, legislation and biodegradation to minimise their adverse impacts.**

**Keywords**: aquatic environment, endocrine disrupting chemicals, Lake Victoria, oestrogens, vitellogenin

## Introduction

Xenoestrogens are substances that are similar in chemical composition and structure to steroidal oestrogens, hence they mimic and compete with them, e.g. by binding onto the hormonal receptors in animals such as fish (Roszko et al. 2018; Kanda 2019). In female vertebrates, oestrogens occur in three major forms; oestrone (E1), 17β-estradiol (E2) and estriol (E3), and serve as primary reproductive hormones (Burgos-Aceves et al. 2016; Ashfaq et al. 2019). These hormonal substances have C18 steroidal groups, which are characterised by tetracyclic molecular frameworks of cyclopentane, phenol and two cyclohexanes. Interestingly, this conformation also forms the four ring structures of xenoestrogens (Khanal et al. 2006). The structures of the three hormones (E1, E2 and E3) are named based on the conformational arrangement on C16 and C17. For example, the structure of the 17β-estradiol has two hydroxyl groups, one at position C3, and the other at the 17β position (Figure 1). Therefore, based on the presence of hydroxyl groups, estradiol has been named as E2. E2 is the predominant female sex hormone produced in follicles of ovaries and it is used specifically in vertebrates for the development and maintenance of reproductive tissue, bone, fat and hepatocytes. The E2 synthesis in ovarian follicular cells involves the production of androstenedione, which is converted into oestrone by aromatase and finally into estradiol through a process catalysed by a series of different enzymes (Cui et al. 2013). Moreover, the liver is another site for biosynthesis of the natural oestrogens; it is also the main site for their further biotransformation. Once the oestrogens are synthesised by aromatase in the liver, they are released into circulation. However, in vertebrates, including fish, oestrogens are taken up again by the liver where they are biotransformed into different metabolites under series of enzymes.

The quantity and specific type of oestrogen excreted naturally in animals varies, depending mainly on the animal's physiology, reproductive cycle and age. For example, pregnant women and lactating mothers discharge approximately five mg $d^{-1}$ of 17β-estradiol (Guang-Guo et al. 2002; Khanal et al. 2006), whereas prenatal dairy cows may excrete up to 11.4 mg $d^{-1}$ of 17α-ethinylestradiol (Khanal et al. 2006). Furthermore, at least 7.0 µg oestrone, 15.2 µg estriol, and 2.4 µg 17β-estradiol have been estimated to be excreted in urine daily by a young woman at the end of the lactating period (Adlercreutz et al. 1986; Liu et al. 2004). As such, oestrogens are continually flushed down in wastewater from homes, hospitals, and abattoirs, and drain into the natural aquatic ecosystems, such as lakes and rivers (Table 1). For pharmaceutical and medical purposes, steroidal estrogenic chemicals like 17α-ethinylestradiol,


17 β-estradiol Estrone Estriol 17 α-ethenylestradiol Stibestol

Coumestrol Isoflavanoid Genistein Zearalenone Fisetin

Diethylphthalate Polychloronated biphenyl Methoxychor Dichlorodiphenyltrichloroethane

**Figure 1:** Natural oestrogens (upper row); phytoestrogens (middle row); industrial xenoestrogens (lower row)

mestranol and diethylstilboestrol are formulated in oral contraceptives and other medications for the treatment of human and animal diseases (Sumpter 1995; Toppari et al. 1996; Augustine and Ander 1998; Guang-Guo et al. 2002).

Xenoestrogens (also referred to as environmental oestrogens) are commonly found in industrially manufactured products, such as fertilizers, canned foods, toothpastes, detergents, parabens, lotions and perfumes (Bhandari et al. 2015). Other products include contraceptives: D-norgestrel and norethindrone (Labadie and Budzinski 2005); plasticizers: phthalates; plastic chemicals: bisphenol-A (BPA) (Oehl et al. 2008); insecticides: aldrin, dichlorodiphenyltrichloroethane (DDT), dieldrin and toxaphene; multiple chemical usage: polychlorinated biphenyls (PCBs); herbicides: metolachlor, alachlor and atrazine (Soto et al. 1991; Campbell et al. 2006); and heavy metals (Hachfi et al. 2012). These substances often leach, drain into and contaminate the environment, in particular aquatic ecosystems, with several adverse impacts (Nandong et al. 2005; Dumitrescus et al. 2010). For example, it is estimated that the concentration of non-steroidal xenoestrogen BPA leached from plastic containers is 139 mg g$^{-1}$ when in contact with water for two weeks at room temperature (Yamamoto and Yasuhara 1999; Mathieu-Denoncourt et al. 2015). Besides, metallic containers release higher BPA, compared with plastics or paper containers. Liao and Kannan (2013) reported that when exposed, intake of BPA from canned foods is 63.6 and 58.6 ng kg$^{-1}$ d$^{-1}$ for teenagers and adults, respectively. Furthermore, the interference of the reproductive system of female vertebrates (such as fish) by xenoestrogens, even in minute quantities, i.e. ng l$^{-1}$ may alter their physiology, endocrine systems and reproductive functions. In the aquatic environment, toxicity in fish results from the potential of xenoestrogens to interfere with oestrogen, androgen and thyroid hormone activities. The toxicity of endocrine system also causes the dysfunction of other organ systems that are under endocrine regulation, such as neurological, cardiovascular and immune systems (Schug et al. 2011; Jordan et al. 2016). Release of xenoestrogens into the aquatic systems should be minimised, because they compromise the reproduction of the aquatic organisms therein, including fish that are an important source of proteins and income for humans. This paper reviews the adverse impacts of xenoestrogens on aquatic ecosystems, such as the disruption of fish endocrine system, vitellogenin (VTG) production, interference with the reproductive cycle and intersex. A detailed understanding of the chemical nature of xenoestrogens and related compounds is necessary for designing control measures that would prevent their adverse environmental impacts, ensure their safe use and control.

### *Vitellogenin production in fish*

Under estrogenic stimulation and regulation, mature egg laying female vertebrates and some invertebrates synthesise VTG (Emmersen and Petersen 1976). The structure of VTG has a dimeric molecule and approximate size of 300–600 kDa (Booth and Skene 2006). In vertebrates like fish, upon elicitation of parenchymal liver cells by oestrogens either as xeno-agonists or xeno-antagonists on the oestrogen receptor, VTG is secreted and thereafter transported in the bloodstream towards the ovarian cells (final destination), where it is required for proper physiological development of oocytes (Jones et al. 2000). The normal level of VTG circulating in the mature females is between 100–1 000 mg ml$^{-1}$, however, in the mature male, its production is less than 20 ng ml$^{-1}$ (Tyler et al. 1996). Therefore, in males and

**Table 1:** Proximity of the natural discharge sources to river and reproductive effects observed on fish species: DDT = dichlorodiphenyltrichloroethane, EDCs = endocrine disrupting chemicals, EE2 = ethinylestradiol, Nm = not measured, PCBs = polychlorinated biphenylsbiphenyls, STP = sewage treatment plant, VTG = vitellogenin WTP = waste treatment plant, WWTP = wastewater treatment plant

| Species | Sex | Rivers | Discharge source | Distance (km) | Observed effects | Conclusion | Reference |
|---|---|---|---|---|---|---|---|
| Spottail shiners | M | St. Lawrence | Montreal city | 50 | High intersex fish | Estrogenic contamination | (Aravindakshan et al. 2004) |
| Spottail shiners | M | St. Lawrence |  | 50 | high hepatic VTG mRNA |  |  |
| English sole | M | Urban rivers | Industrial discharge | Nm | high VTG levels | Contaminants effects observed | (Johnson et al. 2008) |
| English sole | M | Near-urban | Surface runoff | – | rare intersexuality | Contaminants effects |  |
| English sole | M | Non-urban | sewer outfall | – | oocytes atresia | Contaminants effects |  |
| English sole | M | Non-urban | STP | – | altered spawning | Contaminants effects |  |
| Carps | M/F | Ebro Rivers | Zaragoza STP | 20 | low gonado-somatic index | Effects of PCBs, DDT | (Lavado et al. 2004) |
| Carps | M/F | Ebro River |  | 20 | plasmatic VTG | Effects of PCBs, DDT |  |
| Carps | M/F | Ebro River | – | 20 | depress testosterone levels | Effects of PCBs, DDT |  |
| Carps | M/F | Ebro River | – | 20 | alterations in gonads | Effects of PCBs, DDT |  |
| Thicklip mullet | M/F | Basque coast | Gernika STP | Ns | intersex gonads | Endocrine disruption response in males | (Bizzaro et al. 2014) |
| Wild carps | M/F | Anoia River | Sewage treatment | 23 | increased VTG | Observed plasmatic VTG | (Sole et al. 2003) |
| Wild carps | M/F | Anoia River | industrial waste | 23 | increase sex hormones | Observed hepatic VTG |  |
| Thicklip mullet | M/F | Basque coast | industrial waste | – | intersex | Effects of EDCs |  |
| Chub | M/F | Drome River | Urban wastewater | Nm | High VTG | Estrogenic response in wild fish | (Flammarion et al. 2000) |
| Chub | M/F | Moselle River | industrial waste | – | High VTG | – |  |
| Flounder | M | Tokyo Bay | Industrial waste | 40 | testicular oocytes | Abnormal VTG and oocytes | (Hashimoto et al. 2000) |
| Flounder | M | Hokkaido | sewage effluent | 40 | high serum VTG | EDC in bottom feeding fish tissue |  |
| S. Redhorse | M/F | St.Clair River | Stag Island WTP | 26 | VTG in males | $EE_2$ bioaccumulation | (Al-Ansari et al. 2010) |
| S. Redhorse | M/F | St.Clair River | Corunna WWTP | 26 | – | – |  |
| Tilapia | M | Oume River | Calavi-Bonou | Nm | VTG in males | pesticides in tissue | (Okoumassoun et al. 2002) |
| Tilapia | M | Oume River | – | – | – | declined fish stock |  |
| Tilapia | M | Oume River | – | – | – | Pesticide correlates VTG |  |

**Table 2:** Reproductive effects of contaminants on wild fish species from rivers in different parts of the world: Abbreviation; US rivers (S = Susquehanna River; P = Savannah River; C = Columbia River; C = Colorado Rivers; R = Rio Grande River; A = Apalachicola River; M = Mississippi River; M = Mobile River), Pennsylvania Watersheds (D = Delaware River; O = Ohio River; S = Savannah River), *n* = number of sample, Nm = parameter is not measured during the study, APEs = Alkylphenol ethoxylates, OP = Octylphenol, NP = Nonylphenol

| Study area | Location | Fish species | *n* | Males | VTG males | Reproductive effect (%) | *n* (%) | Contaminants | References |
|---|---|---|---|---|---|---|---|---|---|
| Escambia River | USA | *Micropterus salmoides* | 41 | 15 | 3(15) | Increase liver size | Nm | Nm | (Orlando et al. 1999) |
| US Rivers (SPCCRAMM) | USA | *Micropterus salmoides* | 816 | 390 | Nm | Intersex male | 70(18%) | $E_2$, PCB | (Hinck et al. 2009) |
| US Rivers (SPCCRAMM) | USA | *Micropterus dolomieu* | 160 | 70 | Nm | Intersex male | 23(33%) | *p,p*-DDD, *p,p*-DDE | Hinck et al. (2009) |
| US Rivers (SPCCRAMM) | USA | *Cyprinus carpio* | 1 572 | 774 | Nm | Intersex female | 1(0.1%) | *p,p*-DDD, *p,p*-DDE | Hinck et al. (2009) |
| US Rivers (SPCCRAMM) | USA | *Ictalurus punctatus* | 86 | 42 | Nm | Intersex male | 3(7%) | *p,p*-DDD, *p,p*-DDE | Hinck et al. (2009) |
| Pennsylvania Watershed (DOS) | USA | *Micropterus dolomieu* | 240 | 118 | 100% | Intersexuality | 100% | estrone, atrazine, E2 | (Blazer et al. 2014) |
| Crosswicks Creek | USA | *Cyprinus carpio* | 11 | 11 | 5 µg ml$^{-1}$ | Vitellogenic male | 6 | Nm | (Stansley and Washuta 2007) |
| Passaic River | USA | *Cyprinus carpio* | 10 | 10 | 3.04 µg ml$^{-1}$ | Vitellogenic male | 1 | Nm | Stansley and Washuta (2007) |
| Spruce Run Reservoir | USA | *Cyprinus carpio* | 9 | 9 | 0.9 µg ml$^{-1}$ | Vitellogenic male | 2 | Nm | Stansley and Washuta (2007) |
| Lake Apopka | USA | *Gambusia holbrooki* | 60 | 60 | Nm | Increased liver size | | Nm | (Toft et al. 2003) |
| Yukon River | USA | *Esox Lucius* | 155 | 69 | 0.19 mg l$^{-1}$ | Artresia | 10% | PCB, *p,p'-DDT* | (Hinck et al. 2007) |
| Rogue River | USA | *Acipenser medirostris* | 78 | 41 | Nm | Intersexuality | 0% | Nm | (Molly and Daniel 2007) |
| Columbia River | USA | *A. transmontanus* | 174 | 86 | 140 µg dl$^{-1}$ | Hermaphrodites | 3(86) | Aldrin, BHC, DDT | (Feist et al. 2005) |
| Brosna River | Ireland | *Rutilus rutilus* | 7 | 7 | Nm | Intersex male | 1(7) | Nm | (McGee et al, 2012) |
| Inny River | Ireland | *Rutilus rutilus* | 11 | 11 | Nm | Intersex male | 3(11) | Nm | Mc Gee et al. (2012) |
| Suck River | Ireland | *Rutilus rutilus* | 10 | 10 | Nm | Intersex male | 1(10) | Nm | Mc Gee et al. (2012) |
| Deel River | Ireland | *Rutilus rutilus* | 18 | 18 | Nm | Intersexuality | 0 | Nm | Mc Gee et al. (2012) |
| Ballyfinboy River | Ireland | *Salmo trutta* | 13 | 13 | Nm | Intersexuality | 0 | Nm | Mc Gee et al. (2012) |
| Clogdiagh River | Ireland | Salmo trutta | 13 | 13 | Nm | Intersexuality | 0 | Nm | Mc Gee et al. (2012) |
| Woodford River | Ireland | *Salmo trutta* | 17 | 17 | Nm | Intersexuality | 0 | Nm | Mc Gee et al. (2012) |
| Ross River | Ireland | *Salmo trutta* | 6 | 6 | Nm | Intersexuality | 0 | Nm | Mc Gee et al. (2012) |
| Lake Ontario | Canada | *Morone americana* | 27 | 16 | 9(16) | Intersex male | 8 | Nm | (Kavanagh et al. 2004) |
| Grand River | Canada | *E. caeruleum* | 1 031 | 410 | Nm | Intersex male | 16 | Nm | (Bahamonde et al. 2015) |
| Dore River | France | *Gobio gobio* | 56 | 34 | 98 000 ng ml$^{-1}$ | Intersex gonads | 36 | Nm | (Sanchez et al. 2011) |

**Table 2:** (cont.)

| Study area | Location | Fish species | *n* | Males | VTG males | Reproductive effect (%) | *n* (%) | Contaminants | References |
|---|---|---|---|---|---|---|---|---|---|
| Solway Firth River | England | *Platichthys flesus* | 10 | 2 | 20% | Intersexuality | 0 | Nm | (Lye et al. 1997) |
| Tyne estuary | England | *Platichthys flesus* | 54 | 27 | 60% | Intersex male | 53 | Nm | (Lye et al. 1997) |
| Tyne estuary | England | *Platichthys flesus* | 62 | 62 | Nm | Abnormal sperm tail | 100 | Nm | (Gill et al. 2002) |
| Tyne estuary | England | *Platichthys flesus* | 62 | 62 | Nm | Abnormal sperm head | 43 | Nm | (Gill et al. 2002) |
| Lake Eleyele | Nigeria | *Tilapia guineensis* | 83 | 55 | Nm | Intersex gonads | 33 | PCB, dieldrin | (Adeogun et al. 2016) |
| Luvuvhu River | South Africa | *O. mossambicus* | 129 | 129 | Nm | Ovotestis | 57 | PCB, Zinc | (Barnhoorn. et al. 2010) |
| Tokyo Bay | Japan | *P. yokohamae* | 273 | 130 | 2 200 ng ml$^{-1}$ | Intersex male | 15 | APEs | (Hashimoto et al. 2000) |
| Haihe River | China | *E. elongates* | 42 | 20 | 99.4 µg ml$^{-1}$ | Vitellogenic male | 14 | BPA, OP, NP | (Shao et al. 2005) |
| Haihe River | China | *Carassius auratus* | 35 | 16 | 336.7 µg ml$^{-1}$ | Vitellogenic male | 13 | BPA, OP, NP | (Shao et al. 2005) |
| Lake Van | Turkey | *Chalcalburnus tarichi* | 159 | 44 | Nm | Abnormal testes | 6 | Nm | (Unal et al. 2007) |
| Ebro River | Spain | *Cyprinus carpio* | 51 | 31 | 1.8 mg ml$^{-1}$ | Vitellogenic male | 4 | Nm | (Lavado et al. 2004) |

juvenile fish, VTG synthesis and production is abnormal (Bahamonde et al. 2013), with the quantity produced usually correlating with the burden of xenoestrogens or other environmental contaminants in water and sediment (Sumpter and Jobling 1995; Jobling et al. 1998; Denslow et al. 1999; Jones et al. 2000; Van der Oost et al. 2003; Matozzo et al. 2008; Frey et al. 2011). Induction of VTG in wild male fish populations provides evidence for the widespread contamination of the aquatic environment. Globally, estrogenic chemicals, typically ethinyl estradiol from pharmaceuticals are responsible for the abnormal VTG in males (Jordan et al. 2016).

Globally, in lakes and rivers, fish physiology, endocrine system and reproductive functions are often adversely affected by diffuse chemical contaminants and pollutants from various sources (Table 2). The proximity of aquatic ecosystems to both urban settlements and wastewater treatment facilities make them natural recipients of various xenoestrogenic chemicals (Table 1), that may induce synthesis of VTG in male and juvenile fish (Purdon et al. 1994; Harries et al. 1997; Jobling et al. 2002b; Gross-Sorokin et al. 2006; Johnson et al. 2008; Bahamonde et al. 2015; Jarque et al. 2015). Over fifty non-steroidal chemicals that mimic steroidal oestrogens in many species of fish are found in aquatic ecosystems. Indeed, thousands of other chemicals and metabolites in the environment are classified as endocrine disruptors, because of their interference with the functions of endogenous reproductive hormones (Ritchie et al. 2005; Iversen 2018; Miller et al. 2018).

Such chemical metabolites may enter into the bodies of fish through dermal contact, via the gills and by food ingestion. Notable studies on effects of xenoestrogens on alterations in reproductive function have been conducted on *Oncorhynchus mykiss* in Lake Ontario, Canada (McMaster 2001); *Oncorhynchus mykiss* reared in cages installed near sewage treatment outfalls in the United Kingdom (UK) (Purdon et al. 1994); and wild *Rutilus rutilus* and *Perca fluviatilis* in the Hessian River Rhine catchment (Allner et al. 2010). Furthermore, the effects of xenoestrogens and other chemicals on reproductive defects in fish have been observed in the Elbe River, Germany, (Markus et al. 2002) and several UK rivers (Harries et al. 1997). In addition, the potential of the xenoestrogens to disrupt reproductive systems of wild fish have been studied in both laboratory and field experiments in Europe and Asia.

At a concentration of 0.1 ng l$^{-1}$, 17α-ethinylestradiol induced VTG production in male *O. mykiss* (Labadie and Budzinski 2005). Furthermore, because of 17α-ethinylestradiol, several studies in fish confirmed drastic decrease of gonadotropins, reduction of egg fertility, reduced fecundity, atrophy of gonads, embryo mortality, feminization of males and intersex (Harries et al. 1997; Mathiessen et al. 1998; Matthiessen and Sumpter 1998; McMaster 2001; Andersen et al. 2003; Lavado et al. 2004; Feist et al. 2005; Jobling et al. 2006; McGee et al. 2012; Blanchfield et al. 2015).

At a concentration of 5.0 ng l$^{-1}$, estradiol induced the production of female specific proteins in male *Oryzias latipes* (Khanal et al. 2006). In several species of fish, various biological changes resulting from exposure to xenoestrogenic substances have been reported, e.g. intersexuality in *Gobio gobio*, common bream fish (*Abramis brama*), and *Platichthys flesus* (Jobling et al. 1998; Allen et al. 1999; Hecker et al. 2006); inhibited testicular growth in male *O. mykiss* (Jobling et al. 1996); ovotestis in *O. latipes* (Getsfrid et al. 2004); increased liver size in *O. mykiss* (Herman and Kincaid 1988); intersexuality in *Tilapia guineensis* (Adeogun et al. 2016) and testicular oocytes in catfish (*Clarias gariepinus*) (Asem-Hiablie et al. 2013b). Although many feminised male fish can reproduce, their fecundity may be reduced by up to 76% (Sumpter and Jobling 2013). The extent of wild fish population recovery from exposure to synthetic xenoestrogens was tested in whole lake experiments using *Pimephales promelas* population in Lake Ontario (Blanchfield et al. 2015). Whole-lake contamination by 17α-ethinylestradiol had previously collapsed *P. promelas* population (Blanchfield et al. 2015). However, after ceasing the contamination for seven consecutive years, the level of VTG and reproductive abnormalities were reverted to a baseline level (Blanchfield et al. 2015). Because fish is globally one of the most important protein sources in human diet (Obiero et al. 2015; Obiero et al. 2019), it is imperative that chemicals that induce undue VTG production in juvenile females and males and disrupt reproduction be monitored closely, regulated and controlled with all due capabilities and resources.

Intersexuality among fish species, which is the simultaneous presence of female and male gonadal tissue, at the same time in a fixed-sex species is accepted as a significant result of exposure to xenoestrogens in the aquatic environment (Bahamonde et al. 2013). There is increasing research on the intersex conditions among the wild fish population in developed countries. The alarming increase in the detection of ovotestis, testiova, imposex and testicular oocyte conditions are observed among gonochoristic teleosts inhabiting chemically contaminated sites of the aquatic environment (Table 2). Furthermore, reports of intersexuality show either feminization (oocytes within testicular tissue) or masculinization (spermatogenic cells within the ovarian tissue) conditions among teleost fishes (Sardi et al. 2015a; Grilo and Rosa 2017; Hicks et al. 2017). The effects of intersexuality resulting from exposure to xenoestrogenic contaminants include delayed spermatogenesis and oogenesis in males and females, respectively (Bahamonde et al. 2015). Therefore, control of xenoestrogens and related chemical compounds is essential for the maintenance of healthy fish diet, as well as balanced male and female populations in aquatic ecosystems (i.e., the oceans, lakes and rivers) in order to ensure stable populations and productivity.

### *Detection and quantification of vitellogenin in fish*

The techniques used for detection and quantification of VTG vary across experimental designs. The validity of the results is primarily determined by the strength of the method used (Coady et al. 2017). Methods that are well described allow for replication and credibility of studies (Ågerstrand et al. 2011). In the ecotoxicological studies, VTG in fish can be used as an indicator of aquatic ecosystem pollution. Therefore, a wide range of methods for VTG assay in fishes have been extensively reviewed, aimed at reporting the current state of knowledge on threats posed to aquatic ecosystems and fish reproduction by xenoestrogenic chemicals. Samples taken from the fish blood plasma, blood serum, liver and whole body homogenates, may be used for the detection and quantification of VTG using different techniques, with examples herewith. In European flounders fish (*P. flesus*) exposed to effluents from sewage treatment works, Lye et al. (1997) used electrophoresis and scanning densitometry; Fukada et al. (2001) used chemiluminescent immunoassay for masu salmon (*Oncorhynchus masou*), rainbow trout (*O. mykiss*), cutthroat trout (*Oncorhynchus clarki*), white-spotted char (*Salvelinus leucomaenis*), and Sakhalin taimen (*Hucho peryyi*); Shao et al. (2005) used high performance liquid chromatography (HPLC) on the crucian (*Carassius auratus*) and sea catfish (*Enchelyopus elongates*); Allner et al. (2010) used an immunostaining technique for roach (*R. rutilus*) and perch (*P. fluviatilis*), whereas several authors (Emmersen and Petersen 1976; Copeland et al. 1986; Allen et al. 1999) used radioimmunoassay on *P. flesus* and *O. mykiss*.

The advancement in molecular biology and biotechnology has made real time polymerase chain reaction (RT-PCR) useful for the detection of VTG mRNA expressions in fish (Crowther 2001; Islinger et al. 2002). Furthermore, the use of enzyme-linked immunosorbent assays (ELISAs) has demonstrated high degree of acceptability as gold standard assays, because it is considered safer, compared with radioimmunoassays (Crowther 2001). Herein follows the different types of ELISA techniques that have been used for VTG detection in fish: Sandwich ELISA in Japanese medaka fish (*O. latipes*) (Nishi et al. 2002); competitive ELISA in wild gudgeon fish (*G. gobio*) (Sanchez et al. 2011); non-competitive ELISA in freshwater tilapia (*Oreochromis niloticus*) primary cultured hepatocytes (Liu et al. 2007); direct ELISA developed for the smallmouth bass (*Micropterus dolomieu*), white sucker fish (*Catostomus commersonii*) and redhorse sucker fish (*Moxostoma carinatum*) (Blazer et al. 2012; Blazer et al. 2014); and capture ELISA in common carp (*Cyprinus carpio*), bass fish (*Micropterus salmoides*), bullhead catfish (*Ameiurus nebulosus*) and walleye fish (*Stizestedion vitreum*) (Folmar et al. 2001b; Baldigo et al. 2006). Indeed, VTG ELISA kits for many species of salmonids, *O. mykiss*, *O. latipes*, fathead minnows (*P. promelas*), and *C. carpio* have been developed, evaluated and are available commercially (Tatarazako et al. 2004; Jensen and Ankley 2006; Stansley and Washuta 2007). Collectively, the afore-mentioned techniques for the detection of VTG in fish have proven the role of xenoestrogens in their induction and production. Xenoestrogens in polluted aquatic systems raise the levels of VTG in fish. However, VTG production was found to be high in both less and more polluted areas for Nile tilapia (0.77 ± 0.08 mg $l^{-1}$), Nile perch (0.73 ± 0.09 mg $l^{-1}$) and lungfish (0.55 ± 0.06 mg $l^{-1}$) in Lake Victoria (Badamasi et al. 2019). In addition, a value of 0.9 mg $l^{-1}$ VTG in *Esox lucius* from polluted Yukon River, USA, was recorded (Table 2). Such knowledge is vital when formulating, implementing, or reviewing environmental policies, laws and regulations required for maintenance of healthy aquatic and terrestrial ecosystems.

### *Natural sources of xenoestrogens*

Phytoestrogens are plant-derived natural secondary metabolites, belonging to the classes of lignans, isoflavones, and coumestans that act as xenoestrogens by mimicking the actions of endogenous steroidal oestrogens in animals (Chen et al. 2016). Phytoestrogens that are found in a variety of plants (e.g. soybeans, rice, wheat and barley) include genistein, zearalenone and isoflavonoides (Palmer and Palmer 1995; Campbell et al. 2006), which are vital in plant reproduction. Generally, phytoestrogens have similar structures to oestrogens, enabling them to firmly bind onto their receptors in animals (Latonnelle et al. 2002; Lund et al. 2004; Primiani et al. 2019). Those natural organic products are not a threat by themselves, besides helping in the maintenance of normal bone density in animals (Rietjens et al. 2017; Masoodi et al. 2019). However, fish are exposed to phytoestrogens from toxic algae, mycoestrogens (produced by fungi) together with the truly synthetic compounds (industrial chemicals), hence creating estrogenic effects on reproduction and development (Tyler et al. 1998; Houtman 2010; Dellafiora and Dall'Asta 2017).

### *Industrial chemicals as sources of xenoestrogens*

After the discovery of the insecticidal properties of DDT in 1939 by Paul Muller, it proved to be very effective in agriculture and was widely used as an insecticide (Slowikwoska-Hilczer 2006) in the control of vectors of diseases, such as malaria (Van Den Berg et al. 2017; Abong'o et al. 2018). In addition, several industrial chemicals, such as phthalates (plasticisers), BPA (plastic material), aroclor (used in electrical appliances), metolachlor (herbicide), and heavy metals used widely by humans have xenoestrogenic properties (Darbre 2018; Henkel 2018). These chemicals may distort fish reproduction and development (Miccoli et al. 2017). In particular, organochlorine related chemicals, such as DDT, have been reported to have altered the hormonal levels, influenced gonads, and led to the intersex conditions of many species of alligators in Lake Apopka (Florida, USA) (Guillette et al. 1994; Guillette et al. 1995a; Guillette et al. 1995b). Because of their adverse environmental impact, use of these chemicals is closely monitored, and some of them, such as DDT, having been totally banned.

### *The fate of xenoestrogens in the environment*

Several factors determine the fate of xenoestrogenic chemicals in the environment, i.e., physico-chemical properties (e.g. solubility index, redox potential, partition coefficient, hydrophobic-hydrophilic potential, and ability to bioaccumulate), as well as environmental factors (e.g. pH, temperature, salinity and humus content) (Tijani et al. 2016). In wastewater treatment plants, xenoestrogens may be converted into harmless forms, such as water and carbon dioxide, through biological and physico-chemical processes, or be adsorbed and retained onto sediments. Furthermore, aerobic and anaerobic bacteria are able to bio-degrade BPA, with a half-life of approximately three to four days (Tijani et al. 2016). Some pharmaceuticals, such as iodoarene and diazepam, undergo photodegradation, whereas others are unaffected, e.g. phthalates and tetracycline (Tijani et al. 2016). Metabolites of xenoestrogens that are not removed from treatment plants are often persistent in both terrestrial and aquatic ecosystems. Relatedly, although xenoestrogenic chemicals may undergo degradation in the environment, new releases regularly replenish them, lessening net removal.

### *Sources and impact of xenoestrogens on fish reproduction*

Xenoestrogens are endocrine disrupting chemicals (EDCs) that are generated mainly from terrestrial ecosystems through human activities/establishments (e.g. manufacture of pharmaceutical products, herbicides and pesticides) and waste treatment plants. Given that aquatic ecosystems occur at the lowest gradients in an environment, they usually receive runoff deposit, hence, exposing aquatic organisms to adverse impacts of EDCs. Accumulation of xenoestrogens in aquatic ecosystems is exacerbated by the fact that they include a wide range of synthetic chemicals with complex molecular structures; hence conventional wastewater treatment plants have not been designed to eliminate xenoestrogens completely (Kumar et al. 2012). Categories of EDCs include plastic materials, insecticides, herbicides, contraceptives and heavy metals. Fish are considered ideal sentinels, because they respond to EDCs; for example their males show feminization, reduction of milt quantities and sperm density (Jarque et al. 2015). Through dysregulation of normal reproductive processes in animal uteri (e.g. tissue differentiation, growth and maturation of foetuses), EDCs often cause reproductive malfunctions, such as intersex variation (Rich et al. 2016). A congenital condition, intersex variation include anatomical abnormalities in which reproductive organs of an animal is hermaphroditic, hence being neither exclusively male nor female.

Xenoestrogens are globally widespread, and their impacts may be caused by very low concentrations, in the range of subnanometric (sub-nM) levels (Jarque et al. 2015). Conversely, oestrogens are essential for normal regulation of reproduction, bone formation and maintenance, and also cerebrovascular functions (Hurley et al. 2016). It is therefore important to isolate the sources of EDCs in the environment in order to understand associated trends of endocrine related diseases (Hurley et al. 2016). However, in aquatic ecosystems, EDCs occur in different proportions and mixtures, with individual chemicals often acting as either agonists or antagonists of one another (Laetz et al. 2015) or by overshadowing one another. Indeed, in situations where there are mixtures of different EDCs in water, it may be impossible to isolate the adverse effects of individual ones on respective organisms (Tijani et al. 2016).

Wagenaar and Barnhoorn (2018) reported adverse impact of eutrophication and chemical pollution on health of freshwater fishes, i.e. *C. gariepinus and C. carpio* in South Africa. Histopathology alterations e.g. inflammatory responses, circulatory disturbances, regressive changes and foci of cellular alterations (liver); hyaline droplet degeneration and eosinophilic cytoplasm and melanomacrophage centres (kidney); and telangiectasia, epithelial lifting and hyperplasia (gills) were attributable to hyper-eutrophic freshwater habitats. However, gonads neither suffered histopathological changes, nor were any intersex changes observed among the fishes. Several *in vivo* studies carried out in the UK rivers demonstrated adverse effects of different chemicals on fish reproduction; for example, on *O. mykiss* (Purdon et al. 1994; Jobling et al. 1998); *R. rutilus* (Jobling et al. 2002a; Sardi et al. 2015b); wild male *P. flesus* (Hashimoto et al. 2000); male *C. carpio* (Lavado et al. 2004; Thibaut and Porte 2004; Stansley and Washuta 2007); English sole fish (*Parophrys vetulus*) (Johnson et al. 2008) and male spottail shiners fish (*Notropis hudsonius*) (Aravindakshan et al. 2004).

In juvenile female and male fish, the presence of VTG is considered as a biomarker of exposure to oestrogens. The impacts of EDCs may be chronic in nature and multigenerational in extent (Lee et al. 2017). For example, among the biological responses that anthropogenic perfluoroctanesulfonic acid (PFAA) mixtures had on *O. latipes* in three generations during a period of 238 days were sex ratios, hatching and survival rates, fecundity, VTG expression, growth indices, and changes in the histopathology of liver and gonads (Lee et al. 2017). In laboratory experiments, evidence of VTG induction in males has been recorded using model fish species, such as *O. mykiss* (Bon et al. 1997), flounders fish (Folmar et al. 2001a) and rare minnow fish (*Gobiocypris rarus*) (Zha et al. 2007). Furthermore, exposure of juveniles and females of the common goby fish (*Pomatoschistus microps*) to different concentrations of PCB-77, estradiol and dichlorodiphenyldichloroethylene (DDE) (resulting from breakdown of DDT) for 21 days showed VTG levels in liver and gonads corresponding with concentrations of chemicals applied (Dias et al. 2014). Sogbanmu et al. (2018) exposed *C. gariepinus* broodstock to sublethal concentrations of naphthalene, phenanthrene and pyrene, the result showed that biomarker toxicity effect of phenanthrene was the most toxic. The exposure of *P. promelas* to 17β-estradiol (10–100 ng $l^{-1}$) and oestrone (9.9–993 ng $l^{-1}$) inhibit testicular growth, and increase plasma VTG in a concentration-related manner (Panter et al. 1998). Furthermore, when *O. mykiss* was injected with 17α-ethinylestradiol, there were significant dose-dependent increases of VTG, protein plasma, calcium and somatic indices (Verslycke et al. 2002). Similarly, when juvenile mosquito fish were fed with 17α-ethinylestradiol, they exhibited induced VTG production, with increasing exposure (Angus et al. 2005). Relatedly, exposure of *O. latipes* to nonylphenol, phthalates, and BPA results into adverse impact on fecundity and hatching rates (Shioda and Wakabayashi 2000).

When assessment was done to detect and quantify oestrogens (i.e., oestrone, estradiol, estriol and ethinyl estradiol) in Paris (with the then population of approximately 10 million inhabitants), it was found to range between 2.7 and 17.6 ng $l^{-1}$ in wastewater treatment plant facilities, and 1.0 and 3.2 ng $l^{-1}$ in rivers (Cargouet et al. 2004). In the human population of Paris during that period, 30% of the people in the age category of 14–46 were estimated to be females, 36% of whom frequently used oral contraceptives. This situation would explain the relatively high quantities of oestrogen in the environment (Cargouet et al. 2004). Indeed, in France, high levels of the synthetic oestrogens, 17α-ethinylestradiol and alkylphenols were detectable in ground and surface waters at high concentrations (Cargouet et al. 2007). Considering that exposure of male fish to as little as 0.1 ng $l^{-1}$ of oestrogen may induce VTG production (Cargouet et al. 2004; Nash et al. 2004), concerns abound over the then observed concentrations in the Paris environment.

In North America, the St. Lawrence River and the Puget Sound lowlands receive both domestic and industrial wastes from Montreal city, with nonylphenol and β-sitosterol recorded in sediment in lowlands (Johnson et al. 2008). High levels of VTG and intersexuality have been recorded in male *P. vetulus* in the Puget Sound lowlands, attributable to xenoestrogens (Aravindakshan et al. 2004). Similar studies in Europe on the occurrence of BPA in water and sediment samples in Elbe River from Schmilka at the German-Czech border confirmed increased plasma VTG and prevalence of hermaphroditism in male trout (Heemken et al. 2001; Vadja et al. 2008).

In Lake Eleyele, Nigeria, 33% of the Guinean tilapia (*Tilapia guineensis*) exposed to wastewater presented intersex, and males were more affected than females (Adeogun et al. 2016). Furthermore, concentrations of plasma luteinizing hormone and estradiol, mRNA levels of the VTG and zona radiata proteins were found to be significantly higher in males, compared with females. Conversely, PCB congeners (81, 123 and 138), and dieldrin were detected in sediment and fish muscles (Adeogun et al. 2016). Relatedly, Lake Apopka in USA is highly contaminated with chemicals, compared with the reference lakes Orange and Woodruff (Toft et al. 2003). Studies showed that male mosquitofish from Lake Apopka, had shorter gonopodia, and 47% fewer sperm cells per milligram in the testis, when, compared with the reference lakes (Toft et al. 2003). Samples of male blackchin tilapia fish (*Sarotherodon melanotheron*) from contaminated sites in Benin had plasma VTG, which correlated to the levels of organochlorine pesticide in the tissue (Okoumassoun et al. 2002). In Japan, the Tokyo Bay received up to 4.7 $km^3$ $y^{-1}$ of domestic and industrial effluents during the period 1997 to 1998 (Hashimoto et al. 2000). When 192 male flounders (impacted site = 130, control site = 62) in this bay were investigated (1997 to 1998), high concentrations of VTG in males, and three intersex conditions were recorded at impacted sites, unlike at the control site on Hokkaido whose conditions were all normal.

In another study, average concentration of 17α-ethinylestradiol in 50% of shorthead redhorse fish (*Moxostoma macrolepidotum*) collected downstream a wastewater treatment plant at Stag Island, St. Clair River, Canada were 1.6 ng $l^{-1}$ and 1.43 ng $l^{-1}$ in males and females, respectively. Furthermore, concentration of 17α-ethinylestradiol correlated to total body lipid contents of respective fish specimens. However, at the control site, located 24 km from Stag Islands, at Port Lambo, 17α-ethinylestradiol was not detected in the fish (Al-Ansari et al. 2010). Meanwhile, in Alaska, melting snow and industrial runoffs add contaminants to the Yukon River. Studies on the northern pike (*Esox lucius)* in the Yukon River showed that the concentration of VTG in male specimens from contaminated sites were higher than 0.01 mg $ml^{-1}$, likely attributable to exposure to xenoestrogens (Hinck et al. 2007). Downstream of wastewater treatment plants in Irish rivers where *R. rutilus* and brown trout (*Salmo trutta*) were studied (McGee et al. 2012); and the Grand River basin in Canada where the Rainbow dater fish (*Etheostoma caeruleum*) was studied (Bahamonde et al. 2015), intersex was recorded, attributable to exposure to xenoestrogens. The level of VTG in male wild *C. carpio* in Spain sampled downstream Zaragoza's sewage treatment plant was found to be high, attributable to ethinylestradiol and alkylphenols polyethoxylate (Purdon et al. 1994; Lavado et al. 2004). In France, the induction of VTG in wild chub fish (*Leuciscus cephalus*) was investigated in a relatively clean river (Drôme), and another contaminated by metals and organic wastes (Moselle River). Athough serum VTG was not detected in male chub fish of the Drôme River, high levels (>1 mg $ml^{-1}$) were observed in both males and females of the Moselle River (Flammarion et al. 2000). In the Escambia River (USA), the largemouth bass (*M. salmoides*) only showed VTG production in males sampled from sites contaminated by industrial wastes (Orlando et al. 1999). Similarly, in the Pennsylvania (USA) watersheds, plasma VTG was detected in male fish *M. dolomieu* and *C. commersonii* sampled from sites that were contaminated by effluents from a wastewater treatment plant (Blazer et al. 2014). The studies reviewed show that exposure of fish to xenoestrogens result into different reproductive abnormalities, hence necessitating regulation and control of their sources.

### *Bioaccumulation and biomagnification of xenoestrogens in the food web*

Some EDCs have long half-lives in the environment, e.g. ranging between 9–15 years for dioxins in soils (Rich et al. 2016; Nieder et al. 2018), and therefore tend to bioaccumulate and biomagnify in the food web (Rich et al. 2016). Actually EDCs are often lipophilic, and tend to bioaccumulate in the fatty tissues of fish, eventually biomagnifying in the food chain. Besides, metabolites of xenoestrogens are often more potent than their parent compounds (Priac et al. 2017). By virtue of their position in the food web, humans, birds and other consumers of aquatic organisms are vulnerable to EDCs (Daghrir and Drogui 2013). Concerns therefore arise regarding risks associated with fish consumption, depending on concentrations of EDCs in fillet, the quantity consumed, and reproductive stage during exposure. Indeed, in the 1960s, high rates of sterility and spontaneous abortions were recorded in grey seals (*Halichorerus grypus*), and ringed seals (*Phoca hispida*) in the Baltic Sea in association with high concentrations of DDT and PCBs, resulting from consumption of contaminated fish (Rich et al. 2016). At high levels of exposure to EDCs, combinations of adverse forms of reproductive malfunctions may cause decline in whole populations of organisms. Although, reproduction in fish usually occurs whenever the progeny has certain chances for survival, exogenous agents (xenoestrogens) interfere with the normal physiological function of the surviving progeny.

Like in fish, EDCs may have similar adverse reproductive impacts in humans, including decline in conception rates, lower sperm counts, reduced fertility and latent menopause (Rich et al. 2016). They exert their impacts through interference with the hypothalamic-pituitary-gonadal pathway, and regulation/control of the hormonal cascade during development from puberty to adulthood. Although exposure to EDCs may be evident during the foetal stage or infancy, normally, there are no observable effects until puberty or adulthood (Rich et al. 2016). Besides reproductive malfunctions, EDCs have been associated with obesity and growth of cancerous tumours (Jarque et al. 2015). However, in contrast to aquatic organisms, such as fish, the effects of xenoestrogens on humans are less clear, because it is a less studied subject (Tijani et al. 2015). Furthermore, research on the impact of xenoestrogens on human health is limited, because of lack of technical expertise to determine detection limits and the extremely high cost of undertaking risk assessments (Tijani et al. 2015). Epidemiological risk assessment of EDCs on human populations is therefore necessary to comprehend their health impacts and to design effective management measures (Tijani et al. 2015). Although studies on EDCs are scanty in developing countries, there is evidence that they are on the rise in some jurisdictions, such as South Africa (Sorensen et al. 2015).

### *Spatial and temporal variation of xenoestrogens in the environment*

The concentrations of natural and synthetic oestrogens in receiving aquatic ecosystems vary at a spatial and temporal scale, depending on the levels of wastewater inflow, season, population density and human activities in the catchment. Furthermore, xenoestrogens, industrial chemicals and other pollutants may be discharged in relatively high and harmful concentrations in domestic and industrial wastes. For example, in China, the concentrations of nonylphenol, octylphenol and BPA detected in both domestic and industrial wastes correlated strongly with levels recorded in the recipient holding-lake (Jin et al. 2013). Relatedly, in a study of groundwater reservoirs in the USA, it was found that almost 81% of the 47 reservoirs in 18 states were contaminated with pharmaceutical and industrial chemicals (Barnes et al. 2008).

Naturally, bacteria in the environment, particularly in wastewater holding facilities convert harmful chemicals into less toxic forms. However, xenoestrogenic substances and related chemicals do not undergo complete biodegradation, even in wastewater holding facilities with high biomass of bacteria. Furthermore, biodegradation of xenoestrogens often produce metabolites that conventional waste treatment processes and wetland cleansing mechanisms may not completely eliminate (Teske and Arnold 2008). Indeed, anaerobic biodegradation pathways of such chemicals often produce stronger and more potent metabolites that hinder additional degradation (Nandong et al. 2005). The exposure of wildlife to EDCs is intermittent, because of seasonal changes and variable biological, industrial and agricultural activities, and it is possible that fish may be more affected by periodic peak exposure than by chronic exposure (Luzio et al. 2016). Therefore, the production, use and disposal of xenoestrogens and related chemical compounds should follow stringent standard protocols, in order to limit their levels in the environment to non-detectable and non-harmful concentrations and ensure integrity of both aquatic and terrestrial ecosystems.

### *Control of xenoestrogens and related contaminants in the environment*

Because of the adverse environmental impacts of xenoestrogens and related chemicals, concerns abound globally, especially among industrialists, pharmacists, medical professionals, scientific community, public officials and international organizations regarding their safe use and eventual presence in the environment. Several measures are necessary at national and international levels, by different categories of stakeholders to limit the levels of EDCs in the environment and prevent their adverse impacts on both aquatic organisms and humans. The Persistent Organic Pollutants Treaty of 2001 (the Stockholm Convention), as well as the Berlaymont Declaration of 2013, aims at protecting aquatic organisms and humans from adverse effects of EDCs. Conversely, in 2013, the Human Reproductive Health and General Environment Network (HURGENT) was formed in Europe in collaboration with the World Health Organization (WHO) to control adverse effects of EDCs, through surveillance and information sharing. In order to ensure safety of global aquatic ecosystems, the United Nations' Sustainable Development Goals (SDGs) emphasise restoration of life below water (Goal 14), and responsible consumption and production (Goal 12). Furthermore, the European Union placed the contraceptive 17α-ethinylestradiol among the list of priority contaminants (Sumpter and Jobling 2013) to be closely monitored and controlled. Meanwhile in the USA, several chemicals considered to disrupt animal endocrine systems or reproduction and have adverse environmental impacts were banned since the 1970s. Indeed, more than 70 000 potential endocrine disruptors are closely regulated in the USA through the Toxic Substances Control Act (TSCA), the Environmental Protection Agency (EPA) and Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC) (Vlachogianni et al. 2010). However, in developing countries, several factors, e.g. poor sanitation, poor management of industrial, municipal and domestic wastes, poor application methods of herbicides and agro-chemicals, as well as weak implementation of environmental laws are responsible for discharge of large quantities of several chemicals (including xenoestrogens), with adverse impacts on the environment. Because aquatic ecosystems receive cocktails of xenoestrogenic chemicals from several sources, e.g. wastewater treatment plants, agricultural lands and municipal runoff, there is necessity to design effective control measures, advised by surveillance, biomonitoring and ecotoxicological studies. Setting minimum discharge limits for individual chemicals in wastewater and carrying out sensitization of the public regarding their pathways and negative health impacts is also essential. Indeed, redesign of wastewater treatment plants should cater for removal of EDCs, for example, through advanced oxidation technologies.

Tijani et al. (2016) recommend collaborative and multidisciplinary research to collect data on the sources of xenoestrogenic chemicals, their pathways, effects on organisms and humans, and other aspects of EDCs to devise means of regulating their concentrations in the environment and prevent harmful effects on organisms. Amongst these measures is banning the use of some xenoestrogenic chemicals. Relevant environment policies and laws should be formulated and enacted by the line agencies of national governments and other international jurisdictions to control use of xenoestrogenic chemicals. Governments should in turn establish and implement effective enforcement measures of the policies and laws regulating EDCs. Specialised laboratories to study effects of EDCs, and carry out environmental monitoring should be built and equipped, especially in developing countries. Furthermore, the fate of EDCs in the environment should be tracked through design and development of predictive models to assist enforcement of regulatory control measures. Because various stakeholders with conflicting interests produce, use or treat and dispose different types of xenoestrogenic chemicals, political will and support from relevant government authorities, civil societies and non-governmental organizations are prerequisites for effective implementation of control measures against EDCs. In highlighting the environmental challenges posed by xenoestrogens, we hope to raise awareness and indeed design effective control measures, especially for developing countries of eastern Africa, such as Uganda. Implementation of the recommended measures is essential to prevent proliferation of xenoestrogenic chemicals in the environment, for substantial removal from terrestrial ecosystems, and prevention of disruptive effects on endocrine system of aquatic organisms and humans.

### *The requirement for investigations on the impact of xenoestrogens in developing countries*

Most recorded studies of adverse effects of xenoestrogens in aquatic ecosystems (Table 2) have been in developed countries of Asia, Europe and America. Several sub-Saharan African (SSA) countries are using DDT, lindane, heptachlor, endrin, dieldrin and toxaphene for combating agricultural pests and controlling disease vectors, especially mosquitoes. Such practices are represented by the accumulation of toxic chemical residues in different environmental samples, more than any other regions in the world (Mansour 2009). However, limited studies on the impact of xenoestrogens in the aquatic environment and on fish reproduction in developing countries have been undertaken in SSA, e.g. Ghana (Asem-Hiablie et al. 2013a), Benin (Okoumassoun et al. 2002; Agbohessi et al. 2015), South Africa (Marchand et al. 2008) and Nigeria (Adeogun et al. 2016; Ibor et al. 2016; Ibor et al. 2017). Yet, developing SSA countries have serious challenges related to pollution and contamination of their aquatic ecosystems, attributable to poor treatment and disposal of wastes emanating from domestic, municipal, industrial and agricultural sources.

Eastern Africa's Lake Victoria, the world's second largest freshwater lake has been severely affected by organic and inorganic chemical pollution, attributable to unregulated human activities and ill-planned rapid urbanization within its catchment. The level of organic pollution in Lake Victoria has reached the extent of anoxia, with massive algal blooms and general deterioration in water quality. Fortunately, the level of PCBs in water, sediments and fish tissue of Nile perch (*Lates niloticus*) and Nile tilapia (*O. niloticus)* are still within permissible levels recommended by the European Commission (Ssebugere et al. 2014), hence not yet a threat to human health. Similarly, levels of mercury and other heavy metals in water, sediments and fish tissue are also still within permissible international levels (Campbell et al. 2003). However, information regarding a broad range of xenoestrogenic chemicals and VTG in fishes from Lake Victoria is lacking. This paper reviews critical literature at global level to set the platform for experiments and field investigations aimed at assessing the levels and adverse impacts of xenoestrogens in Lake Victoria, with emphasis on *L. niloticus*, *O. niloticus* and lung fish (*Protopterus* spp.), as the main fisheries.

## Conclusions and recommendations

Xenoestrogenic chemicals include a broad of range of compounds that disrupt the vertebrate endocrine system by mimicking and interfering with their functions in reproduction, resulting into abnormalities, such as testicular oocytes, infertility, low fecundity and intersexuality. Vitellogenin production in male fish is an important biomarker, indicating xenoestrogenic exposure in aquatic environments. A cocktail of substances, such as plastic materials, domestic and industrial wastes, pharmaceutical drugs and agro-chemicals are important sources of xenoestrogenic chemicals that are carried in effluents or runoffs from terrestrial to aquatic ecosystems. Being an organism that reacts to the effects of xenoestrogens, fish serves as a sentinel, providing evidence of the adverse impacts of the chemicals on vertebrate reproduction. Many of the chemicals bio-accumulate in fish fatty tissues because they are lipophilic, hence potentially biomagnify in the food web, through consumption by humans and other predators like birds. Although evidence is scarce, there are indications that xenoestrogens may cause similar reproductive abnormalities in humans, as observed in fish. At a population level, adverse effects of xenoestrogens on fish reproduction cause a decline in their numbers or localised population extinction of the species (Hamilton et al. 2016). In contrast to well-studied adverse impacts of xenoestrogens on aquatic ecosystems and fish in developed countries, similar studies are lacking in developing sub-Saharan African countries, such as those in the African great lakes region. Therefore, to inform studies on xenoestrogens in Lake Victoria, this paper reviewed critical literature regarding their adverse impacts on fish, such as vitellogenin induction. There are several control and management measures required to stem the adverse impacts of chemicals on reproductive biology of fish and ultimately to humans. These include surveillance, reproductive studies on fish and other aquatic and terrestrial organisms, collaborative research, sharing critical information and banning of their production and use. Such efforts require strong political will, formulation of national/international management policies, laws, and convention, and their enforcement by relevant government authorities and agencies.

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