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A Comprehensive Review of Current Environmental Pollutants of Pharmaceutical, Agricultural and Industrial Origin

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Abstract

The health effects of low level, chronic exposure to environmental contaminants include the development of antibiotic resistance, endocrine disruption, and carcinogenicity amongst other issues in aquatic, terrestrial, and human species. Presently unknown quantities and mixtures of potentially hazardous compounds accumulate in the environment having severe effects on numerous species. Wastewater treatment plants are not designed to remove these contaminants meaning that treated water contains an array of pollutant compounds unless they are intrinsically prone to biodegrade or have hydrophobic combinations. The impact of this continued pollution and accumulation not only threatens animal and human life, but it also represents a major threat to environmental sustainability having dire consequents for ecosystems. As the human population continues to expand the issues of environmental pollution, destruction of ecosystems, loss of biodiversity, and soil infertility will become increasingly more prominent. This review aims to highlight key pollutants impacting on environmental and human health.

Keywords: Pollutant; Health effect; Bioaccumulation, Toxicity; API; POPs

Introduction

Environmental pollution is a major cause for concern globally, as the adverse impact of pollutant chemicals on aquatic, terrestrial, animal, and human health becomes increasingly difficult to escape. Indeed, environmental sustainability is now a primary world health goal as climate change, safe water scarcity, crop infertility, biodiversity loss, and depletion of natural resources all pose challenges to food security and ultimately population survival. Chemical pollutants in the environment relate to pharmaceutical, Personal Care Products (PPCPs), industrial and agricultural chemicals that have been identified as causing adverse effects in the environment and its diverse ecosystems, biotic and abiotic. The EU Water Framework Directive has added pharmaceuticals including antibiotics, anti-inflammatories, and medically prescribed hormones to the 'watch-list' of chemicals posing a threat to aquatic environments together with insecticides, herbicides and sunscreen [1]. Indeed, since the International Conference on Chemicals Management (ICCM) 2015, it is now recognized that the environment also requires protection from pharmaceutical products. Assessing the impact of all environmental pollutants on biotic and abiotic life is key to understanding their role in disrupting ecosystems, though it is impossible to establish the exposome of exposure for each ecological niche. Pesticide, industrial, domestic waste, pharmaceutical, PCPs, and their metabolite by-products are consistently introduced into the environment where the complex mixtures accumulating in abiotic areas is undetermined. Issues relating to this include biotic toxicity, bioaccumulation, slow degradation, water and air transportation, and environmental persistence. The effect of such pollution on human health has been investigated for certain compounds where adverse health effects such as perinatal disorders, infant mortality, respiratory disorders, hypersensitivity, carcinogenicity, cardiovascular disease, mental disorders amongst others have been identified [2]. Astonishingly there are approximately 30,000 chemicals currently in use which can potentially enter the environment during manufacture, processing, or use, alarmingly with less than 1% have been subject to a detailed toxicological investigation [3]. Individuals are becoming more environmentally aware as the devastating impact of environmental destruction becomes unavoidable and quality of life is put at risk. As such increasing numbers of people are resolutely and systematically communicating concern about pollution and sustainability with a demand for ecological governance. This review aims to provide insight into prevalent and important agents of environmental pollution, their routes of entry, ecological impact, and risk to human health. While major efforts have been implemented to clean up the environment, concrete action requires a detailed understanding of the magnitude of the problem. As such the authors endeavor to provide an unambiguous understanding of the relationship between human health and its absolute dependence on environmental safety (biotic and abiotic) and sustainability.

Active Pharmaceutical Ingredients

Active Pharmaceutical Ingredients (APIs) have become an essential part of life as numerous types are consumed at an unquantifiable rate globally. As such the APIs, their metabolites, and conjugates, which are primarily excreted in urine or faeces gain entry to the aquatic and terrestrial environments from the manufacture, formulation, processing, clinical and domestic waste [4]. Studies show the manufacture of pharmaceuticals causes concentrated regional accumulation of APIs with global pollution a consequence of contaminated wastewater at concentrations of milligrams per liter (mg/L) when wastewater discharges are not sufficiently controlled at facilities [5]. Pharmaceuticals are typically developed to be fat-soluble enabling transfer across biological membranes with therapeutic intent, but this also contributes to an accumulation in biotic aquatic life.

Antibiotics

The unregulated anthropogenic use of antibiotics has led to the accumulation of antibiotics, Antibiotic-Resistant Bacteria (ARB) and Antibiotic-Resistant Genes (ARG) in the environment from medical, veterinary, and personal use. Hotspot reservoirs of ARGs and ARBs include areas of repeated exposure to antibiotic APIs such as hospital, animal housing areas, aquaculture operations, and Wastewater Treatment Plants (WWTPs) [6]. While Antimicrobial Resistance (AMR) is not a manmade phenomenon, the prevalence, emergence and re-emergence of bacterial infectious disease with subsequent repeated doses of often ineffective antibiotics has enabled the extensive proliferation of antibiotic resistance species within the environment. Indeed, as a consequence of such overuse and misuse, resistance to the major antibiotics colistin and third-generation cephalosporins (critical prophylactic drugs) has emerged **(Table 1)**. Residual levels of antibiotics in aquatic and terrestrial systems from agricultural run-off, domestic and clinical sewage and wastewater varies depending on the drug molecule, characteristics such as polarity, resistance to degradation, metabolism in vivo and the duration of therapy. Tetracyclines, fluoroquinolones, macrolides (tylosin), and sulfonamides are frequently observed in manure at higher concentrations than other antibiotic classes [7] where they can hurt vertebrates and amphibians. Additionally, studies have shown that fluoroquinolones, macrolides, and tetracyclines affect chloroplastic and mitochondrial protein synthesis, plastid replication, morphology, and photosynthesis in plants [8]. Due to their aquatic habitat, fish are particularly exposed to environmental API pollution with the bioaccumulation of antibiotics already well established [9] **(Table 1)**.

Table 1: Maximum detected residual levels (n.d.=not determined) in aquatic (µg/L) and terrestrial (µg/kg) systems, physiochemical interactions (P-PC=pseudo-partitioning coefficient; Koc=Soil Organic Carbon-Water Partitioning Coefficient; pKa=Acid dissociation constant) and ecotoxicity of selected antibiotics.

Antibiotic	Route of Entry	Application	Maximum Detected Residual Levels				Physiochemical Interactions	Adverse Effects
			Soil µg/kg	Manure µg/kg	Surface Water µg/L	WasteWater µg/L		
Fluoroquinolones (FQs)								
CIP (2nd generation)	**Medical**	**Human use** Treatment of genitourinary, respiratory and gastro enteric infections. 500 mg twice daily for 7 d-14 d (may be longer dependent on infection)	5,600 [7]	45,000 [7]	42 [8]	32,000 [8]	Amphoteric molecules High sorption to soil/ sediment (high *Koc* and *P-PC*) Considered immobile Nevertheless, high solubility coefficients in water [7] Partially metabolized, up to 50%-90% excreted by animals, where Transformation products (TPs) can be back-transformed to potent parent compound [8] Extended half-lives in soil (months to years) [10] TPs may be even more stable and toxic to ecosystems than the parent compound [11].	Toxic effects towards *Cyanobacteria*, algae crustaceans, earthworms, frogs, fish which include inhibition of the neurotransmitter γ-aminobutyric acid, central nervous system excitement, convulsions, arthropathy, cardiovascular malfunctions, ocular problems, gastrointestinal disturbances and reproductive dysfunction [12-15] Presence of residual levels in tissues of fish, primarily in the muscles [16], due to lipophilic character of FQs. Selective pressure on bacteria that
MAR (3rd generation)	**Veterinary**	**Veterinary use** Administered to cattle, (including lactating dairy cattle) and pigs for treatment of mastitis and respiratory infections at dose of 2 mg MAR/kg bw/day for upto 5 d	n.d	n.d	n.d	n.d		

ENR (2nd generation)	**Food Production** (agriculture and aquaculture)	**Medicated Feed** Growth stimulant, prophylactic agent. The typical dose for fish is about 5 mg ENR/kg-10 mgENR/kg BW for up to 10 d	1,300 [7]	4,700 [17]	0.05 [19]	900 [18]		facilitates the spread of AMR and cross resistance [19] Translocation to the edible parts of plants resulting in phytotoxicity [20] Detection of residues in meat, milk, vegetables and tap water [21,22] above Max Detection Limits (MRLs) Reduced nitrification, dentification and phosphorus uptake in WWTP on exposure to CIP, attenuating vital microorganisms [23]
Sulfonamides (SA) and Diaminopyrimidines								
SMX	**Medical**	**Human use** Most often potentiated with TMP (co-trimoxazole) in a 1:5 ratio (TMP:SMX) for treatment bronchitis, prostatitis and UTIs.	54.5 [7]	178 [24]	6.8 [25]	20.6 [25]	Amphoteric, polar, water-soluble compounds that contain aromatic rings Low to moderate sorption to soil (low P-PC)- Electrostatic interactions favoured sorption mechanism Highly mobile and easily transported to aquatic environment [7] Rapidly absorbed, 10%-40% of parent compound excreted unchanged [24] Dissipation half-lives of 4.7 to 15.1d (top soils) and 65.5 to 152 d (substrates) reported [26]	Toxic to fish, resulting in developmental malformation decreased locomotion ability, disordered organ function and oxidative stress [27] Toxicity to microalgae is also well documented [28] Although weak lipophilicity, their ubiquitous usage can result in residual levels detected in fish [16,29], as well as plants (cucumber, lettuce, tomatoes), which can cause adverse allergic reactions and alterations in the delicate balance of intestinal flora [30] Sub therapeutic doses shown to alter composition of enriched nitrate-reducing microcosms, inhibiting nitrate reduction capabilities [31] and promoting occurrence of ARG. TPs such as N4 - acetyl - SMX and glucuronide conjugates, can be back transformed to SMX in WWTPs [24]
	Veterinary	**Animal use** IM administration to cattle containing 40 mg TMP:200 mg SMX (1 mL/16 kg bw for up to 5 d) for treatment of respiratory, urogenital and soft tissue infections.						
	Food Production (agriculture and aquaculture)	**Medicated Feed** Administered orally or in drinking water/ feed to calves, pigs, horses, poultry and fish (5 mg/kg bw TMP+25 mg/kg SMX for upto 5 d (7 d for fish)						
TMP	**Medical**	**Human use** Co-trimoxazole can also be	Low	480 [22]	0.21 [32]	521.4 [33]	Relatively high-water solubility	TMP has been reported to cause toxicity to bacteria, algae, rotifers,

		used for treatment of Pneumocystis pneumonia in people with HIV/ AIDS					High mobility and low to moderate sorption (low *Koc* and *P-PC*) [32] Partially metabolized (60%-80%) with 20%-40% excreted as metabolites and conjugates in humans. Half-lives vary considerably, with an average of 30 d reported [7]	daphnia, duckweed and fish [28,34] Not particularly lipophilic, however, reported residual levels have been detected in fish [16], meat and milk, exceeding MRLs [20] Also detected in vegetables and drinking water [35], where ARG pose risk to both the environment and consumer
	Veterinary	**Animal use** Co-trimoxazole used for treatment of prostate, urinary tract, respiratory, skin and soft tissue infections in cats and dogs. Typical dosage 15 mg/kg every 12 h PO.						
	Food Production	**Medicated Feed**						
Tetracyclines (TCs)								
DOX (Class 3)	**Medical**	**Human use** Treatment of respiratory, eye, intestinal and urinary infections, acne, gonorrhea, chlamydia, syphilis, periodontitis (gum disease), among others. Typical dosage 100 mg PO every 12 hours for 5 to 10 day	728 [7]	381,000 [20]	0.004 [17]	6750 [36]	Amphoteric structures Possess 3 pKa values-*pKa1*, *pKa2*, and *pKa3* at pH 3.3, 7.7, and 9.7, respectively. Strong sorption to soil-chelating properties enables them to form stable complexes with ions (Ca, Al, Fe etc) [37]. Partially metabolized, more than 70% excreted by animals. TPs can be more toxic than TC parent compound [38]. Extended half-lives ranging from days to years.	Can elicit toxic effects on *Cyanobacteria* (*Microcystisaerugin osa*) [39] and green algae (*P. subcapitata*) [40] at environmentally related concentrations. Kim et el. reports affected gene regulation in *Daphnia magna*, which leads to complex multigeneration carry-over [41]. Malformations in amphibians (*X. tropicalis*) e.g. induced shortened body length and pericardial edema, and zebrafish e.g. yolk sac edema, uninflated swim bladder and dosage-dependent growth inhibition [27]. Residual levels detected in fish and edible parts of plants, negatively effecting plant growth and consumer health, while proliferating AMR [6,18] Interference with biogeochemical cycles-alter dissimilatory NO_3 reduction [42], inhibit phosphorus and COD removal, poly-P accumulation and glycogen synthesis
TET (Class 1)	**Veterinary**	**Animal Use** Used in cattle, pigs, poultry, turkeys, and pets for the treatment of susceptible bacterial infections at a dose of 10 mg/kg-20 mg/kg bw per day, for 3-5 days						
	Food Production (agriculture and aquaculture)	**Medicated Feed** Growth stimulant, a prophylactic agent	2,680 [7]	98,000 [7]	0.06 [43]	12, 200 [44]		

								of the Shewanella strain [38]
Macrolides (ML)								
AZT	**Medical**	**Human use** Used to treat myriad infections including respiratory, skin, ear and eye infections, and sexually transmitted diseases. A typical dose of 500 mg per day for 5 d.	n.d	n.d	0.404 [45]	10,500 [46]	Strong sorption to soil/ sediment (high *Koc* and *P-PC*). Electrostatic interactions are favoured sorption mechanism-binding to manure/soil components increases with a decrease in pH [7]. Low solubility, though often persist in water due to huge usage. Poor absorption in the animal's gut results in >40% of parent compound being excreted [47]. Long term persistence of TY and AZT in soils, with half-lives up to 67 d and 990 d respectively [7].	Toxic effects toward *Cyanobacteria*, algae, duckweed, crustacean, fish and amphibians at sub-inhibitory concentrations [27,37]. Fish are particularly sensitive, where MLs inhibit critical physiological processes, such as development, reproduction, neurological and nervous system function [27,46]. Detection of residues in fish, primarily accumulated in the liver owed to the relatively strong lipophilicity [16]. Residual levels detected in edible parts of plants, posing high risk to consumers as well as resulting in phytotoxicity e.g. inhibit root elongation and seed germination [48]. Sub therapeutic levels also promote the proliferation and spread of ARG [34]. TPs are numerous and result in stable compounds, in similar conc. range as parent molecule, where further understanding of their fate and behavior in the aquatic environment is required [49].
TY	**Veterinary**	**Animal use** Treat bovine respiratory and swine dysentery diseases-IM suspension (200 mg/mL) administered at 8 mg/lbbw for up to 5 d in cattle and 4 mg/lbbw for up to 3 d in pigs. Also used to treat chronic respiratory disease complex in chickens and infectious sinusitis in turkeys.	1, 250 [7]	8, 100 [7]	2.19 [50]	72 [51]		
	Food Production (agriculture and aquaculture)	**Medicated Feed** Growth promoter for poultry, pigs, and cattle as well as fish. Subtherapeutic doses can average 61 d in swine						
Amphenicols								
FLO	**Veterinary**	**Animal use** IM administration at dose of 15 mg/kg-20 mg/kg bw, (with a second dose 48 hours later) in cattle (including lactating cattle), pigs and horses for treatment of respiratory and Pod	6 [52]	n.d.	0.93 [50]	2.84 [53]	Increased sorption for aqueous phase-readily water-soluble and weakly hydrophobic (low *Koc* and *P-PC*) [54]. Highly mobile. Rapidly absorbed in animals, with 69%-89% excreted as metabolites that are markedly more polar in water [55]. Degradation half-lives up to 103 d have been reported in field soil [47].	FLO and TPs are known to induce acute and chronic toxic effects on microalgae, fish, aquatic and terrestrial invertebrates, and aquatic and terrestrial plants [28,55]. Remain bioactive in soil, resulting in phytotoxicity, even under anaerobic conditions [47].

		dermatitis infections.						The occurrence of ARGs, such as the MDR gene *cfr*, which confers resistance to phenicols, as well as unrelated antibiotic groups e.g. lincosamides, oxazolidinones, pleuromutilins, and streptogramin A [56]. Detected in edible plants (lettuce leaves, carrot peel) at concentrations up to 38 µg/kg [57]. Alters the abundance, metabolism and function of nitrogen cycling microorganisms [58].
	Food Production (agriculture and aquaculture)	**Medicated Feed** One of the most widely used antibiotics in aquaculture in Europe, North America, and Asia, administered at a dose of 10 mg kg^{-1} in a period of 10 to 20 days.						
Beta Lactams								
AMX	**Medical**	**Human use** Used to treat tonsillitis, bronchitis, pneumonia, and infections of the ear, nose, throat, skin, or urinary tract. Typical dosage of 500 mg 3 times daily for 7 d (may be longer dependent on infection)	Low	Low	0.31 [58]	6.94 [55]	Highly mobile in soil- having an increased affinity towards the aqueous phase. Presence of beta lactam ring structure makes them highly susceptible to hydrolysis and photolysis. Rapidly absorbed in animals, between 40%-90% excreted unchanged [59]. Half-lives in the soil are low, 0.43-0.57 days for AMX [7].	Toxicity towards microalgae has been documented, though the rate of inhibition is dependent on the antibiotic and strain [28]. The most prominent concern is the enhancement of the occurrence and spread ARG among well-known superbugs such as MRSA, VRE, and ESBL-carrying *E. coli* [8,60]. Detection of beta-lactams in meat, milk, and aquatic products has been reported [20]. Beta lactams can remain bioactive in soil, having adverse effects on Nitrogen and Carbon cycling microorganisms [61].
	Veterinary	**Animal use** Treatment of respiratory, genitourinary, gastrointestinal, skin and soft tissue infections. Typical doses in dogs and cats is 10 to 25 mg/kg, two or three times a day for 5-7 d.						
	Food Production (agriculture and aquaculture)	**Medicated Feed** Growth stimulant, prophylactic agent						

CIP: Ciprofloxacin; MAR: Marbofloxacin; ENR: Enrofloxacin; SMX: Sulfamethoxazole; TMP: Trimethoprim; DOX: Doxycycline; TET: Tetracycline; AZT: Aztreonam; TY: Tylosin; FLO: Florfenicol; and AMX: Amoxicillin

Importantly, even low concentrations of environmental antibiotics promote genetic alterations and the Horizontal Gene Transfer (HGT) of resistant genes, plasmids, and transposons, and altered phenotypic and genotypic diversity amongst species. While issues relating to the transmission and pooling of ARGs within ecosystems are being investigated, the drastic impact on soil microorganisms and soil infertility relating to carbon mineralization and nitrogen cycling [62] must also be fully determined. Additionally, the depletion of environmental bacterial species may encourage an increase in populations of parasite and pathogenic non-bacterial species such as toxic *Cyanobacteria* in aquatic environments [6] with

eutrophication a serious consequence. Furthermore, the impact of the environmental presence of ARB and ARGs on human and animal health associated with the intestinal microbiota and dysbiosis is an important area in need of investigation. Alterations in gut microbial species are known to affect host metabolism, immunity, mental health, and susceptibility to non-communicable diseases such as Inflammatory Bowel Disease (IBD), other autoimmune conditions and cancer [63].

Antidepressants

Antidepressants (ADs) are the most commonly prescribed medication for the treatment of major depressive disorders, sleep disorders, and chronic pain diseases such as fibromyalgia. Antidepressant drugs such as the tricyclic antidepressant amitriptyline, Selective Serotonin Reuptake inhibitors (SSRIs) fluoxetine, Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) duloxetine and Venlafaxine, and monoamine oxidase inhibitors are the most widely prescribed ADs globally. The environmental presence of such ADs from pharmaceutical manufacture and wastewater has demonstrated toxic effects on aquatic organisms. Indeed, the Mode of Action (MOA) of these drug classes relates to binding and inhibiting, presynaptic re-uptake transport proteins [64] essential for nerve functionality, making them non selectively toxic to all species containing a nervous system. Studies show that fish species exposed to minute concentrations of ADs can become more aggressive, less cautious, and display feeding issues at concentrations below toxic to humans [65]. ADs can affect other aquatic fauna including macroinvertebrates essential for ecological niches [66] negatively affecting trophic systems. For example, fluoxetine concentrations upto 1.4 µg/L have been detected in freshwater areas where it has been associated with alterations in reproduction, intracellular signaling pathways, memory, cognitive function, and development in aquatic species [67]. Fluoxetine and its metabolite norfluoxetine have been detected in fish tissue at 10 µg/kg and in brain tissue at a concentration from 0.1 ng/g^{-1} ng/g, indicating bioaccumulation of this compound and its metabolites. This SSRI was found to affect mating behaviours, in male fathead minnow at concentrations of 1 µg/L with aggression, self-isolation, and other behavioural issues at greater concentrations [68] **(Table 2)**.

Therapeutic Hormones

The environmental presence of hormones has been well established as having a deleterious impact on numerous species. Natural hormones 17 β-estradiol (E2), Estrone (E1), and Estriol (E3) and pharmaceutical APIs such as Ethinylestradiol (EE2) and Levonorgestrel has been detected in surface waters at concentrations from ng to µg per liter [69] concentrations known to affect the endocrine systems of many organisms. EE2 is clinically used to treat the menopausal and postmenopausal syndrome, prostate and breast cancer, and the treatment of osteoporosis [70]. Environmental pollution with these hormones induces changes in aquatic life by interaction with hormone receptors. The endocrine system regulates homeostasis, reproduction, behaviour, and the development of species.

Table 2: Detected levels, adverse effects, and aquatic half-life are for common hormones, anti-depressant, and non-steroidal anti-inflammatory drugs found in the aquatic environment.

API	Levels Detected (µg/L)	Adverse Effects	Aquatic ½ Life (Days)
Hormones Estrone Estradiol Ethinylestradiol	**Drinking-Water** Estrone-5 Estradiol-7.5 Ethinylestradiol-37	• Links to breast/prostate cancer [69] • Increases in the feminisation of male fish populations [71] • Bioaccumulate in aquatic organisms • Reproductive issues in animals and issues with plant root development [69]	Estradiol >27 Ethinylestradiol>46
Anti-Depressants Fluoexitine (FLX) Venlafaxine (VFX)	**WWTP Effluent** Fluoexitine-0.929 Venlafaxine-0.214 **Surface Water** Flouexitine-0.54 Venlafaxine-0.045	• FLX has shown behavioural side effects including suicidality, panic attacks and anxiety [72] • FLX can produce context-specific behavioural effects in mosquitofish • Bioaccumulation in aquatic organisms with10 µg/kg detected in fish tissue [68] • VFX side effects in humans include tremor, dizziness and a decreased male sex-drive while it can also disrupt fish behaviour and can impose serious harmful effects on endocrine function [68] • Studies have shown VFX to impact gill metabolism and reduce sodium-potassium ATPase activity in rainbow trout [73]	Fluoexitine>67 Venlafaxine >93
NSAIDS Diclofenac Ibuprofen Naproxen (NPX)	**WWTP Effluent** Diclofenac-0.23 Ibuprofen-3.2 Naproxen-3.4 **Surface Water** Diclofenac-<0.2 Ibuprofen-7.4 Naproxen-5.6	• NSAIDs alter the biochemical and microbial activity of soils potentially affecting fertility [74] • NPX has been detected in fish bile at levels 1000 times higher than surrounding water the [75] • NPX exposure at environmentally relevant levels increases the risk of bioconcentration and thyroid disruption in zebrafish [76] Ibuprofen and Diclofenac at similar levels significantly affected embryo locomotivity and were potentially neurotoxic	Diclofenac-21 Ibuprofen-27 Naproxen-14

The presence of natural and synthetic hormones in the environment can affect the endocrine system of organisms by mimicking endogenous hormones and antagonising or altering the synthesis of endogenous hormones categorising them as Endocrine Disrupting Chemicals (EDCs). Therapeutic and natural hormones gain entry to the environment via wastewater effluent with sludge applied as fertiliser, clinical wastewater, and livestock housing areas. Furthermore, these hormones may bioaccumulate in biota having entered living tissues via multiple uptake pathways with concentrations increasing at each trophic level in fatty tissue and milk. Numerous studies describe the effect of hormone APIs on the reproductive and sterility of fish at trace concentrations. Studies demonstrate that exposure to EE2 in zebrafish induces an increase in vitellogenin (an egg yolk precursor protein and biomarker for estrogen exposure) concentrations and feminization of male fish at concentrations of 10 ng/L, with a decrease in vitellogenin production and masculinization at 50 ng/L of the anabolic androgen 17β-trenbolone [71]. Zebrafish are regularly used in environmental studies as they are robust and spawn continuously allowing laboratory studies housing fish in tanks with contaminant water. In addition to these effects' other issues such as a decrease in gonadal development and altered gonad differentiation, embryonic development alterations, reduced fecundity and/or fertility are also often observed. At the present assessment of EDC toxicity is achieved via short term exposure of small numbers of test organisms giving a monotonic response for analysis with very few studies assessing chronic exposure over entire life cycles and multiple generations. Such studies are certainly warranted as chronic exposure may induce inherited alterations which cannot be determined with non-trans generational studies or impacts causing behavioural, mating, and fertilisation issues. Additionally, EDCs may induce long-term variations in gene expression via altering epigenetic patterns relating to global action, effecting epigenetic regulators and/or their cofactors or gene-specific actions effecting the regulation of locus-specific epigenetic patterns [77]. Long-term EDC studies may also identify recovery of species to disrupting hormones where complete recovery of gonad differentiation was seen for Zebrafish in a full-life-cycle analysis following exposure to 3 ng/L EE2 [78] however, this is concentration-dependent.

Non-Steroidal Anti-Inflammatories

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) particularly ibuprofen, diclofenac, and naproxen are the main analgesics and anti-rheumatic therapeutic drugs in use globally, with concentrations detected in wastewater and connected waterways **(Table 2)** [79]. These therapeutics affect by acting on the inhibition of Cyclooxygenase (COX), essential for eicosanoid metabolism, including prostaglandin synthesis [80]. While important in pain modulation, prostaglandins also have vital functions in the regulation of blood circulation, vascular permeability, and kidney function [81]. Diclofenac appears to induce the highest degree of acute toxicity of all NSAIDs where renal lesions and alterations of rainbow trout gills were detected at the Lowest Observed Effect Concentration (LOEC) of 5 µg/L and minor sub-cellular impacts at 1 µg/L [82]. Additionally, studies show that E2 affected prostaglandin synthesis *in vitro* in trout macrophages at 5 mg/L [83]. Naproxen at concentrations of 12.3 mg/L and 690 mg/L is toxic to green algae and rainbow trout respectively [84] with its derivatives having adverse effects on biota including impairing the lipid peroxidation system of bivalves [85]. NSAIDs are not efficiently removed from WWTPs leading to accumulation in living organisms from their aquatic environment, meaning they are not subject to degradation and are mostly biotransformed. NSAIDs toxicity to algae and microbial species (particularly soil) has also been established, with diclofenac being more toxic to algae and microbial organisms than ibuprofen [79]. Furthermore, microbial biofilms downstream of WWTPs have been shown to accumulate these pharmaceutical compounds with alterations to their microbial functioning in aquatic ecosystems [86].

Industrial Pollution

The environmental impact of industrial pollutants is well established relating to their hepatotoxicity, neurotoxicity, nephrotoxicity, and carcinogenicity. Furthermore, there are abundant industrial and agricultural chemicals now recognised has having the ability to disrupt the endocrine system of numerous aquatic species. These industrial EDCs include alkylphenols (surfactants and detergents), insecticides (organochlorines and neonicotinoids), plasticizers (phthalates, bisphenols, octylphenol), heavy metals (cadmium, nickel, lead) and cosmetic molecules including benzophenones. Industrial compounds regularly associated with aquatic pollution include metals, Polychlorinated Biphenyls (PCBs), Hexa-Chlorocyclohexanes (HCHs), phenolic compounds, and phthalates. Heavy metal toxicity and carcinogenicity results from many mechanistic aspects depending on the pollutant with arsenic, cadmium, chromium, lead, and mercury the 5 main priority metal contaminants from anthropogenic use. The metal cadmium, for example, is frequently detected at parts per billion (ppb) concentrations, where it can induce physiological changes in the gills and kidneys and hypocalcemia of freshwater fish [71]. In humans, heavy metal toxicity relates to cardiovascular diseases, developmental defects, neurologic and neurobehavioral disorders, diabetes, hearing loss, hematologic and immunologic disorders, and carcinogenicity [87]. The first phthalate ester, di(2-ethylhexyl)phthalate (DEHP), was established as a plasticizer for use in the manufacture of hard plastic Polyvinyl Chloride (PVC) in 1930 and is now widely used in toys, food wrapping, latex paints, insecticides and cosmetics amongst other applications. Phthalates have been recognised as having endocrine, mutagenic, carcinogenic, and teratogenic activity [88] and can possibly contribute to endometriosis [89]. In accordance with this, 6 phthalates have been listed as priority pollutants by the Environmental Protection Agency. These compounds enter the environment during manufacture, medical, industrial, agricultural, and domestic use via leaching, migration, and oxidation. Phthalates are known to affect the reproductive systems of aquatic species at concentrations below 10 mg/kg altering the development of reproductive organs, hormone production, metabolic function, and

infertility [89]. The chemical BisphenolA (BPA) used to make polycarbonate plastics used in the food and liquid containers and epoxy resins are known to have oestrogenic effects resulting in endocrine alterations of aquatic species. In recent years it was discovered that leachates from BPA and phthalates have estrogenic effects. Migration from the plastics and containers into surrounding tissues and environments was an important find as it altered the perception of these compounds in terms of their toxicity [90]. Polychlorinated Biphenyls (PCBs) are anthropogenic organic chlorine compounds with a range of industrial applications including sealing and caulking compounds, inks, paint additives, coolants, and lubricants. While removed from use post-1970 due to environmental endocrine toxicity, these PCBs persist, bioaccumulate, bind in soil, and move as particles in water and air making them a current environmental hazard. PCBs are known to be neurotoxic, carcinogenic, and cause infant mortality, birth defects, decreased immunity, and IQ and skin disease [91]. Polycyclic Aromatic Hydrocarbons (PAHs) such as benzo(a)pyrene and bicyclic aromatic hydrocarbons such as naphthalene are ubiquitous organic contaminants resulting from incomplete combustion or pyrolysis of organic material such as coal, oil, and wood and are Persistent Organic Pollutants (POPs). While not produced for industrial applications they are used as intermediaries in the agricultural and pharmaceutical industries. Numerous PAH (16 listed as EPA priority pollutants) are known to be cytotoxic, mutagenic, teratogenic, and carcinogenic with bioaccumulating in fatty tissue due to their lipophilic nature. Human exposure to PAHs is via inhalation of pyrogenic fumes, consumption of contaminated food, smoking, and industrial effluents.

Agricultural Pollutants

Pesticides including the organochlorine insecticides methoxychlor, endosulfan, and heptachlor **(Figure 1)** are known to possess endocrine-disrupting activity. Methoxychlor became commonly used following the ban of DDT due to its environmental persistence, toxicity, and endocrine activity **(Table 3)**. HCHs for example, are organochlorine pesticides and POPs known for their ecotoxicity, persistence, and worldwide accumulation. Fish are known to highly be susceptibility to endosulfan and heptachlor toxicity with Lethal Concentrations (LC50) at ppb concentrations for endosulfan and mg/L for heptachlor [71]. Glyphosphate is an organophosphate phosphonoglycine non-selective herbicide, which became available in 1974 for residential, commercial, and agricultural use. Glyphosate is known to affect the growth and metabolic functions of many unicellular (microbes) and multicellular organisms (algae, invertebrates, annelids, arthropods, amphibians) found in soil and water [92]. As water-soluble herbicide glyphosate does not bioaccumulate but gains entry to the food chain from water sources where it is a significant risk to consumer safety. Glyphosate formulations sold as herbicide products induce membrane disruption, apoptosis, mitochondrial respiration inhibition, and DNA alterations in mammalian cells [93]. The application of inorganic fertiliser to the soil to improve fertility leads to large concentrations of nitrates (NO_3^-) and nitrites (NO_2^-) in water and soil. Livestock production also contributes to environmental pollution with untreated manure, sewage, pollutant emissions, and residual feed particularly medicated feed released into waterways. Nitrate pollution affects drinking water and promotes eutrophication of dangerous algae blooms, high animal mortality due to variations in dissolved oxygen and dead zones in coastal marine ecosystems. Nitrite and N-nitrosamine aquatic pollution are toxic the biotic, abiotic, and human life as it influences many biological functions. Agricultural waste contains animal therapeutic agents such as hormones, NSAIDs, and antibiotics with discarded dairy milk containing large quantities and varieties of microbial species. Land run-off from agricultural applications and livestock feeding is, therefore, a contributor to aquatic and terrestrial EDC, API, ARG, and ARB pollution affecting surrounding waterways. Studies show that agricultural Greenhouse Gas (GHG) emissions including CO_2, CH_4, N_2O, and Fluorinated (F) gases impact global warming [94].

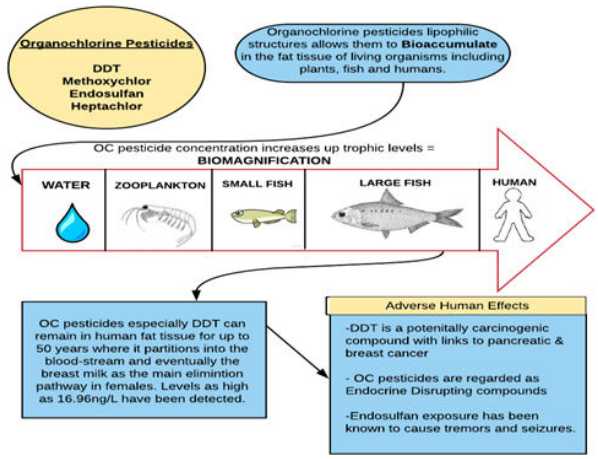

Figure 1: A schematic displaying the biomagnification effect and adverse human effects of pesticide pollutants.

Furthermore, agricultural expansion to provide enough food for the increasing human population is having drastic environmental impacts as ecosystems and biodiversity are sacrificed globally, to support crop and livestock production. Additionally, the use of disinfection biocides in the agricultural and food industries such as Quaternary Ammonia Compounds (QACs), hypochlorite's, iodophors, and chlorine dioxide-based solutions [2] leads to environmental exposure to these compounds. QACs are toxic to numerous aquatic species including fish, algae, microbial species, and daphnids with chlorine and its by-products causing mortality, defects, and reproductive issues to environmental species. Furthermore, AMR is proliferated due to environmental exposure to sub-lethal concentrations of these biocides. Anthropogenic

application of these chemicals relates to WWTPs and the use of livestock manure, discharging into surrounding waterways.

Table 3: Lists the intended purpose and adverse effects caused by the overuse of common Organophosphorus/Organochlorine Pesticides and Fertilisers.

Agricultural pollutant	Intended purpose	Environmental impact
Organophosphorus Pesticides Glyphosate MalathionDichlorvos	Glyphosate Based Herbicides (GBH) are applied to inhibit a specific target plant biochemical pathway [93] Malathion alters thyroid system of fish species affecting growth, behaviour, fitness, and survival [95]	Polyethoxylated amine used in GBH formulation has displayed toxicity to aquatic organisms and animals. Eutrophication resulting in algae blooms, loss of biodiversity, and fish death. Malathion alters thyroid system of fish species affecting growth, behaviour, fitness, and survival [95]
Organochlorine Pesticides 2,4-Dichlorophenoxyacetic Acid (2,4 D) DDT Heptachlor	Applied for the control of insects and weeds from farms to forests. Inhibit biochemical pathways of target plants and insects.	Bioaccumulation Highly POP (Heptachlor ½ Life >2 years) EDCs Impacts on biotic and abiotic [72] Direct exposure to OC pesticides leads to neuromuscular disorders
Fertilisers Organic Synthetic	Nitrogen-rich fertilisers applied to provide nutrients for plant growth in order to ensure maximum yields. Improves soil fertility.	Run-off causes eutrophication Dangerously high nitrate levels in edible foods Nitrate contaminated drinking water has been linked to health defects including blue-baby syndrome [96] Presence of APIs

Conclusion

The quantity and variety of therapeutic, industrial, and agricultural man-made chemicals present in the aquatic environment continue to increase globally with an unmeasured impact on ecological niches. Current OECD and ISO ecotoxicological tests rely on the toxicological impact of test chemicals on the activity of a single species while neglecting the diverse interaction of species within ecosystems. Fish vertebrates are quite sensitive to anthropogenic impacts and pollutants, and as such are often employed as biotic biomarkers in the ecological evaluations of aquatic environments. Consequently, ecotoxicological tests assessing negative impacts on ecosystems combining community parameters need to be established. Research endeavours assessing multi-trophic analysis need to be determined to counteract this issue. It is also important to consider a non-monotonic response of low-level repeated exposure to biotic systems to fully understand the impact of pollutants on the environment and its ecosystems. Determining repeated low-level chronic exposure on terrestrial and aquatic species will better inform real-life exposure and risk analysis. Fervent operations are ongoing to reduce the impact of environmental pollution and reduce the consequences however,extensive damage has already been done. WWTPs are not currently designed to remove therapeutic pharmaceuticals leading to their bioaccumulation in the environment. Bioremediation using microbial species to transform pollutants into inactive compounds shows some promise for cleaning up environmental pollutants such as PAHs. At present, it appears that reducing and mitigating the use of these environmental pollutants is the best approach to reduce their impact, particularly as their toxicity relates to their low-level persistence, bioaccumulation, repeated exposure, and pollutant interactions. Development of alternative organic pesticide options will be key in reducing pollution levels, such methods include the use of bird species in crop areas to consume insects and alley cropping. The bioaccumulation of these toxicants is a serious issue as numerous pollutants have been detected in mammalian milk representing a serious risk to suckling neonates.

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