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Review article

Selected widely prescribed pharmaceuticals: toxicity of the drugs and the products of their photochemical degradation to aquatic organisms

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Abstract
Cholesterol-lowering drugs, antidiabetics, antiarrhythmics, antidepressants, and antibiotics belong to the most prescribed drugs worldwide. Because of the manufacture, excretion, and improper disposal of leftover drugs, the drugs enter waste waters and, subsequently, surface waters. They have been detected in surface waters all over the world, from concentrations of ng/l to concentrations several orders of magnitude higher. Since pharmaceuticals are designed to be both biologically and chemically stable, photochemical degradation by sun radiation represents a way of transformation in the natural environment. This review provides a survey of how selected drugs of the above-mentioned classes affect aquatic organisms of different trophic level. The emphasis is on the harmful effects of phototransformation products, an area of scientific investigation that has only attracted attention in the past few years, revealing the surprising fact that products of photochemical degradation might be even more toxic to aquatic organisms than the parent drugs.

Keywords: Pharmaceuticals; Photodegradation; Toxicity of photoproducts

Highlights:
- Cholesterol-lowering drugs, antidiabetics, antiarrhythmics, antidepressants, and antidiabetics belong to the most prescribed drugs worldwide. They have been detected in surface waters all over the world.
- Since pharmaceuticals are designed to be biologically as well as chemically stable, photochemical transformation by sun radiation represents a way for them to degrade in the natural environment.
- Toxicity of the drugs' photoproducts has begun to attract attention. Several studies have recently revealed that the photoproducts may be even more toxic to the aquatic organisms than the parent drugs themselves.

Introduction

Pharmaceuticals include an enormous group of compounds; the US Food and Drug Administration listed over 20,000 prescription drug products approved for marketing in 2021 (Fact Sheet, 2021). Cholesterol-lowering drugs (hypolipidemic agents), antidiabetics, antiarrhythmics, antidepressants, and antibiotics belong to the therapeutic categories prescribed in the greatest amounts worldwide (Aus der Beek et al., 2016; Mezzelani et al., 2018; Li, 2014).

Globally, the use of pharmaceuticals reached about 3,600 billion doses in 2015 and was estimated to increase by 25% by 2020 (Mezzelani et al., 2018). Moreover, the outbreak of the coronavirus (COVID-19) pandemic in 2019 induced an unprecedented increase in the use of several old and repurposed therapeutic drugs, such as nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic and antimalarial drugs, antiretrovirals, analgesics, and their supporting agents, and even veterinary medicines, *e.g.*, ivermectin (Gwenzi et al., 2022).

Although the remarkable worldwide increase in medicine usage may be considered one of the greatest benefits of modern society, a parallel result of this growing usage is the ubiquitous occurrence of pharmaceuticals in natural ecosystems (Aus der Beek et al., 2016).

Active pharmaceutical ingredients are discharged into the natural environment in many ways, mainly during their manufacture, usage, and improper disposal of unused drugs (Wilkinson et al., 2022). There is evidence that environmental exposure to these substances has detrimental effects on the well-being of ecosystem living constituents (including humans), *e.g.*, by selecting antibiotic-resistant bacteria, feminizing fish, and increasing the susceptibility of fish to predation.

In principle, an environmental transformation of any xenobiotic substance may include processes of biotic (aerobic and anaerobic) and abiotic (chemical) character. Concerning chemical degradation, mainly oxidation, hydrolysis, and/or

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binding to environmental matrices come into consideration (Patel et al., 2019; Sebastine and Wakeman, 2003).

Since pharmaceuticals are designed to be chemically stable (Khetan and Collins, 2007) and wastewater treatment plants have not been tailored to remove micropollutants (substances in the concentration range of ng/l to hundreds of μg/l) of very different solubilities, polarities, and absorption abilities (Khasawneh and Palaniandy, 2021) additional processes are likely to contribute to the environmental fate of pharmaceuticals.

Surface waters are exposed to solar radiation. They typically contain metal ions and some of them, mainly humic waters, also various absorbing species that can act as photochemical sensitizers. In such a system, even recalcitrant xenobiotic compounds may be degraded in photoinitiated processes (Boreen et al., 2003; Klementová et al., 2017, 2019, 2020, 2021, 2022). Thus, in surface waters, photoinitiated processes may represent a noteworthy transformation pathway for such – biologically and chemically resistant – compounds. A physicochemical background of photochemical reactions and a general overview of photochemical degradation of some selected groups of pharmaceuticals covering the different ways of decomposition mechanisms together with the relationship between the photosensitising effect of a drug and its chemical structure is provided in the review of Klelemen et al. (2022). Strategies utilised by medical chemists toward mitigation of phototoxicity risks are given in the overview of Harrison et al. (2023). A general feeling presumes that even a partially degraded drug should be unharmful, or at least less harmful to non-target species than the original drug. Nevertheless, several studies have proven that products of biotic (metabolic) as well as photochemical degradation of various substances may be more toxic to aquatic organisms than the parent compounds themselves (Klementová et al., 2020, 2021, 2022; Tixier et al., 2002, 2009; Traviński and Skibiński, 2022). A better understanding of these processes is essential to a better insight into the fate of pollutants in the natural aquatic environment and the possible effects of parent compounds and their transformation products on aquatic organisms.

Ecotoxicology represents a framework enabling the testing of a compound's impact on organisms and thus revealing, or at least estimating, its potentially harmful effects. There is a large number of methods and organisms used in such assays. In autotrophs, the algae *Chlorella spirulina* and *Desmodesmus subspicatus* are often used because of their simple laboratory maintenance (OECD 201, 2011). OECD 221 (2006) describes toxicity testing using freshwater aquatic plants of the genus *Lemna* (duckweed) – *Lemna gibba* and *Lemna minor*. The cladoceran *Daphnia magna*, a representative of the microcrustacean group, is a flagship in toxicity testing in surface waters (OECD 202, 2004; OECD 211, 2012). The planktonic species *D. magna* has several characteristics which help to easily perform toxicological tests, especially those targeted at acute toxicity: *D. magna* reproduces parthenogenetically when in suitable conditions and can be relatively easily maintained under laboratory conditions. The zebrafish *Danio rerio* represents a common model of vertebrates in ecotoxicology (OECD 203, 2019). The extrapolation of the obtained results to higher vertebrates cannot be simply straightforward and should be done with care. Nevertheless, the response of fish to xenobiotics in general is a significant indicator of manners in which a particular compound (or products of the compound's photochemical degradation) affects fish assemblages in surface waters.

This review aims to summarise the basic data about the impacts of selected groups of widely prescribed drugs (hypolipidemic drugs, antidiabetics, antiarrhythmics, antidepressants, and antibiotics) on aquatic organisms, with a special emphasis on the harmful effects of the products of photochemical degradation of the drugs on the species in the aquatic environment.

The selected groups of drugs and their representatives discussed in this review are synoptically overviewed in Table 1.

Table 1. Selected groups of widely prescribed drugs and their representatives covered in this review

Medical drug class	Representatives
Hypolipidemic drugs	Statins (atorvastatin)
Antidiabetic drugs	Metformin (+ product its wastewater plant degradation guanylurea)
Antidepressants	Sertraline, fluoxetine
Antiarrhythmic drugs	Beta-blockers (metoprolol, atenolol, propranolol) Calcium channel blockers (diltiazem, verapamil) Potassium channel blockers (amiodaron)
Antibiotics	Penicillin antibiotics (amoxicillin) Fluoroquinolone (ciprofloxacin, ofloxacin) Macrolide antibiotics (erythromycin) Tetracycline antibiotics (tetracycline, oxytetracycline) Sulfonamides (sulfamethoxazole – usually used in combination with diaminopyrimidine trimethoprim)

Hypolipidemic drugs

Hypolipidemic, lipid-lowering, drugs, are classified into two groups – statins and fibrates (Pahan, 2006). Statins (*e.g.*, atorvastatin, rosuvastatin, lovastatin, fluvastatin, simvastatin) lower cholesterol by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which catalyses a rate-limiting step in cholesterol biosynthesis; this, in turn, leads to cholesterol biosynthesis suppression (Stancu and Sima, 2001). Fibrates (*e.g.*, clofibrate, bezafibrate) stimulate cellular fatty acid uptake and β-oxidation of fatty acids mainly in peroxisomes and partly in mitochondria (Pahan, 2006).

Atorvastatin (Fig. 1) is one of the most commonly prescribed drugs, *e.g.*, it ranked number one in the number of prescriptions in the USA in 2019 (ClinCalc, 2021a). It has been detected in the aquatic environment worldwide in a range of concentrations – from tens of ng/l to mg/l (Conley et al., 2008; Ministry of Agriculture of the Czech Republic, 2019; Lee et al., 2009; Tete et al., 2020).

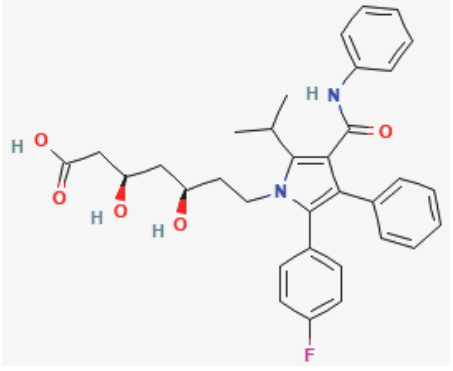

Fig. 1. Structure of atorvastatin (https://pubchem.ncbi.nlm.nih.gov/compound/Atorvastatin)

Falfushynska et al. (2019) studied the effects of atorvastatin in relatively low concentration (1 µg/l) on a marine bivalve *Mytilus edulis*. The exposure to atorvastatin had an impact on energy homeostasis – it led to a significant elevation of the basal metabolic rate (thus depleting body energy reserves), and to the alteration of membrane properties, with the digestive gland being the major target.

Hu et al. (2022) studied the effects of atorvastatin on the physiological parameters and stress-related gene expression in *Daphnia magna*. The authors concluded that short-term (24 h and 48 h exposure to atorvastatin at a concentration of 500 µg/l induced the expression of antioxidant-related genes (*Nrf2, Keap1, HO-1*, and *GCLC*) and apoptosis-related genes (*p53* and *PIG3*) to effectively manage oxidative stress and DNA damage. A chronic toxicity test lasting 21 days revealed that the time to first brood was significantly longer than that in the control group, the number of neonates notably lower, while the heart rate was higher. Swimming behaviour was substantially affected; the higher the atorvastatin concentration the smaller the total swimming distance and the swimming range area.

Ying Han et al. (2022) exposed zebrafish embryos to several statins representatives to evaluate the developmental toxicity of the substances. Statins altered the expression of several fundamental genes, *e.g.*, those involved in heart contractions and calcium ion binding. They also affect the expression of transcription factors and the G protein-coupled receptor signalling pathway.

A study by Klementová et al. (2021) on the water plant *Lemna minor* demonstrated that while atorvastatin itself did not exhibit an observable effect measured as leaf area growth inhibition, exposure to products of photochemical degradation of atorvastatin under light conditions relevant to natural waters led to a significant inhibition in leaf area growth.

Antidiabetic drugs

The treatment of type I diabetes is limited to the application of insulin from an external source either by individual injections or using an insulin pump (Mayo Clinic, 2023), since the pancreas makes little or no insulin.

For type II diabetes, a number of therapeutic approaches exist, mainly using antidiabetic agents. Currently, several major categories of oral antidiabetic drugs are available – they include classes of biguanides and thiazolidinediones acting as insulin sensitizers, sulfonylurea classes that affect insulin secretion, or groups of sodium-glucose cotransporter inhibitors blocking glucose reabsorption in the kidneys (Chaudhury et al., 2017; Dahlén et al., 2022).

Metformin (Fig. 2), a derivative of guanidine from the biguanides group, represents the preferred first-line glucose-lowering drug. It was introduced in the 1990s in Europe and the USA (Bailey, 2017) and in a few years became the most prescribed glucose-lowering medicine worldwide, now being the 3rd–4th most prescribed drug in the USA (ClinCalc, 2023).

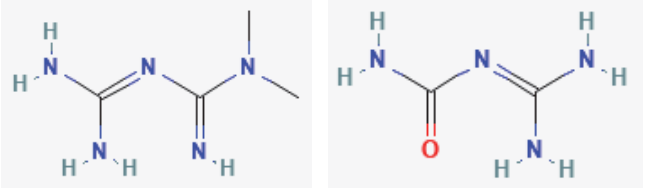

Fig. 2. Structure of metformin – **left** (https://pubchem.ncbi.nlm.nih.gov/compound/Metformin) and guanylurea – **right** (https://pubchem.ncbi.nlm.nih.gov/compound/Guanylurea)

Due to its enormous usage, it has been repeatedly detected in wastewater treatment plant effluents in many countries in Europe, as well as in the USA, Australia, Malaysia (Briones et al. 2016), and China (Yan et al., 2019). Its concentrations in these countries are in the range of tenths to tens of µg/l.

Though beneficial for humans, metformin is considered one of the emerging environmental micropollutants with negative effects on the aquatic ecosystem.

Godoy et al. (2018) studied the toxicological effects of metformin on four organisms of different trophic levels: an aquatic plant *Lemna minor*, an aquatic crustacean *Daphnia similis*, a freshwater cnidarian *Hydra attenuata*, and the fish *Danio rerio*. Effective concentrations at 50% (EC_{50}) found in the study were quite high – tens of mg/l for *L. minor*, *D. similis*, and even higher for *D. rerio* and *H. attenuata*. Nevertheless, the authors concluded that currently recommended standard toxicity assays may result in an underestimation of the adverse effects of substances that affect the endocrine system. Moreover, they highlighted the fact that the number of prescriptions for metformin has been increasing enormously due to almost epidemic levels of people diagnosed with diabetes. Since metformin is not metabolised in the human body and is therefore excreted unaltered (Gong et al., 2012), it belongs to pharmaceuticals most commonly detected in the aquatic environment (Ambrosio-Albuquerque et al., 2021).

Wei et al. (2022) demonstrated that metformin induces multiple antibiotic resistance in *Escherichia coli* at environmental concentrations.

Since metformin was shown to partially undergo aerobic bacterial degradation to guanylurea in sewage treatment plants (Trautwain and Kümmerer, 2011), some ecotoxicological studies of guanylurea were performed. An investigation by Jacob et al. (2019) into the effect of guanylurea on brown trout (*Salmo trutta* f. *fario*) resulted in the conclusion that guanylurea did not lead to lethal embryonic or behavioural consequences in brown trout at the concentrations used in their tests, and that the biochemical markers (namely lipid peroxides and stress proteins) were not influenced.

In their study on the Japanese medaka fish (*Oryzias latipes*), Ussery et al. (2019) demonstrated that guanylurea has similar effects as metformin on growth in the early life stage (decreased fish length and body weight), even in concentrations three orders of magnitude lower in comparison with metformin (ng/l for guanylurea vs µg/l for metformin) and much below the concentrations repeatedly measured for guanylurea in surface waters.

A study by Elizalde-Velázquez et al. (2021) on a zebrafish (*Danio rerio*) revealed that guanylurea delayed the hatching process, induced developmental abnormalities in embryos, increased the activity of antioxidant enzymes and oxidative damage biomarkers in embryos – and thus, even in environmentally relevant concentrations poses a threat to at least some aquatic species.

Antidepressants

Antidepressants, the drugs used to treat not only clinical depression but also other conditions including *e.g.*, obsessive-compulsive disorder, generalised anxiety disorder, post-traumatic disorder, and others (NHS, 2021), belong to several classes (Stöppler, 2023): selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic and tetracyclic antidepressants.

Antidepressants of the SSRIs class have recently been recognised as a major therapeutic advance in psychopharmacology, with sertraline and fluoxetine ranking among the

first twenty most frequently used drugs in the USA (ClinCalc, 2021b, c) and belonging to the most prescribed drugs in European countries as well (Lalji et al., 2021).

The primary mechanism of action of SSRIs is the inhibition of the presynaptic reuptake of serotonin by the serotonin transporter, which subsequently leads to an increase in the amount of serotonin at the postsynaptic membrane in the serotonergic synapse. According to Edinoff et al. (2021), the therapeutic effects of SSRIs cannot be ascribed to the simple inhibition of the serotonin transporter only; it is presumed that some further mechanisms of action contribute to achieve the resulting effect (Edinoff et al., 2021). According to current knowledge, the neuronal stress caused by SSRIs leads to a shift in brain homeostasis, with the result of a downregulation of the serotonin transporter in some areas of the brain and its upregulation in others (Santarsieri and Schwartz, 2015). This mechanism may explain the fact that the full therapeutic effects of SSRIs manifest themselves not earlier than four to six weeks after the treatment initiation, despite significant instantaneous alterations in serotonin flux (Edinoff et al., 2021).

Commonly used antidepressants, such as sertraline and fluoxetine (Fig. 3), have been detected in urban sewage and other environmental water samples throughout Europe, North America, and China (Alonso et al., 2010; Kostich et al., 2014; Lajeunesse et al., 2012; Wu et al., 2015; Yuan et al., 2013). Although the concentrations of the drugs usually do not exceed the low hundreds of ng/l, they may have adverse effects on aquatic organisms.

Yang et al. (2019) investigated the ecotoxicity of sertraline on two aquatic microbial communities, the green alga *Chlorella vulgaris* and the cyanobacterium *Microcystis aeruginosa*. They detected an inhibition of growth and a decrease in chlorophyll-a concentration, which means a reduction in photosynthetic efficiency.

Ribeiro et al. (2015) reported sertraline toxicity on zebrafish (*Danio rerio*) and sea urchin (*Paracentrotus lividus*) embryo bioassays even at environmentally relevant concentrations – they observed embryonic and larval developmental abnormalities.

Calza et al. (2021) investigated the photochemical reaction of sertraline under simulated solar irradiation in the presence of heterogeneous photocatalyst TiO_2. Microtox bioassay using *Vibrio fischeri* was employed in the study to evaluate the ecotoxicity of the photo-transformation products. The authors found that the transformation products exhibited distinctly higher toxicity than the parent molecule.

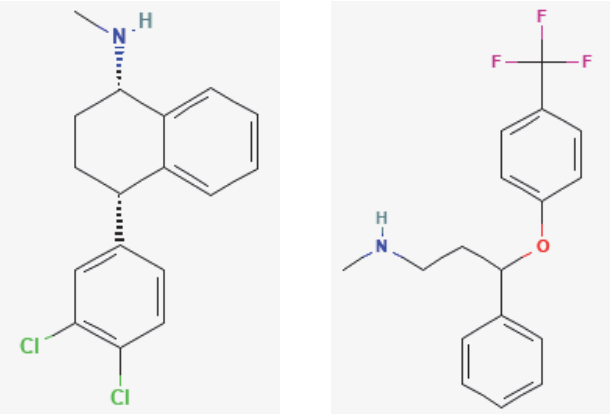

Fig. 3. Structure of sertraline – **left** (https://pubchem.ncbi.nlm.nih.gov/compound/Sertraline) and fluoxetine – **right** (https://pubchem.ncbi.nlm.nih.gov/compound/Fluoxetine)

Ofoegbu et al. (2019) reported that fluoxetine caused concentration-dependent changes in locomotor activity, DNA damage, and a decrease in feeding and fissioning in the planarian *Schmidtea mediterranea*.

De Farias et al. (2019) concluded in their study of the fluoxetine effect on zebrafish embryos that though LC_{50} (concentration that kills 50% of test animals) for embryos is rather high (1.18 mg/l in 168-hour treatment), fluoxetine caused loss of equilibrium (characterised by the fish side-laying at the bottom of the microplate well) and hatching delay in embryos. It also affected their locomotor activity and inhibited acetylcholinesterase in concentrations three orders of magnitude lower.

Pan et al. (2022) observed several adverse effects in their study focused on the toxicity of the fluoxetine photodegradation products formed under UV-A light exposure which was tested on zebrafish (*Danio rerio*) embryos: the hatching time of zebrafish embryos was delayed, the heart rate increased, and the body length decreased. Furthermore, changes in neuron-related and apoptosis-related gene expression were discerned. Their findings highlight the need to consider the toxicity of photodegradation products when assessing the environmental risk of a parental drug.

Antiarrhythmic drugs

Arrhythmias are conditions where the heart rhythms differ from the normal sinus rhythm. These conditions can be the result of a wide range of individual or combined causes (Barton et al., 2020). The medical approach commonly includes the use of antiarrhythmic medication. Antiarrhythmic drugs are categorised into four classes according to the mechanism of action: three of them control the transportation of ions in and out of the cells – calcium-channel blockers, potassium-channel blockers, and sodium-channel blockers. The fourth type of medication, beta-blockers, reduces blood pressure.

Among the drugs most prescribed for arrhythmias, the following rank as most commonly used: the beta-blockers metoprolol, atenolol, propranolol, the calcium channel blockers diltiazem and verapamil, and the potassium channel blocker amiodarone (ClinCalc, 2022). Their structures are visualised in Fig. 4 (metoprolol, atenolol, and propranolol), in Fig. 5 (diltiazem and verapamil), and in Fig. 6 (amiodarone).

Although all of these substances are extensively metabolised in the human body and only small portions of the drugs are excreted unchanged (Brocker et al., 2020; Latini et al., 1984; Talreja and Cassagnol, 2022), they have been repeatedly found in surface waters in concentrations ranging from ng/l to hundreds of ng/l (Batt et al., 2015; de Barros et al., 2018; Iancu et al., 2020; Komesli et al., 2015; Santos et al., 2013).

Aquatic vertebrates, fish, possess beta receptors in their hearts, livers, and reproductive systems, so prolonged exposure to pharmaceuticals belonging to the beta-blockers group (metoprolol, atenolol) may cause deleterious effects as proven in several studies summarised by Santos et al. (2010). These effects include alteration of plasma steroid levels, decreased egg production, and ultrastructural changes in the liver and kidney. Invertebrates cannot be targeted via beta receptors since they do not possess them. Nevertheless, detrimental impacts on these organisms were also observed: a significant reduction in heart rate, fecundity, and biomass in *Daphnia magna* and inhibition of the growth of the green algae *Desmodesmus subspicatus* (Santos et al., 2010).

Allouche et al. (2022) observed a significant change in the taxonomic composition and functional traits of benthic nematodes (*Photis longicaudata* and *Anticoma eberthi*) exposed to diltiazem.

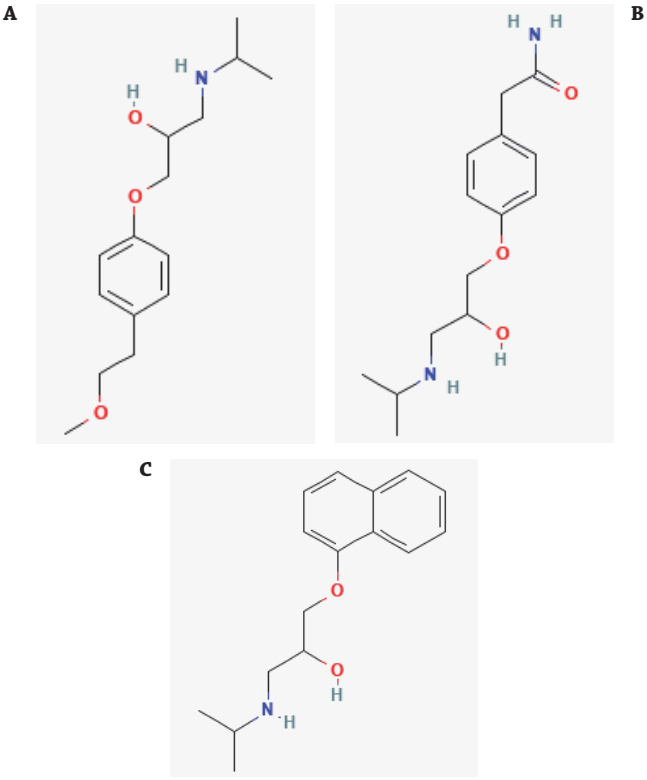

Fig. 4. Structure of metoprolol – **A** (https://pubchem.ncbi.nlm.nih.gov/compo und/Metoprolol), atenolol – **B** (https://pubchem.ncbi.nlm.nih.gov/compound/Atenolol), and propranolol – **C** (https://pubchem.ncbi.nlm.nih.gov/compound/Propranolol)

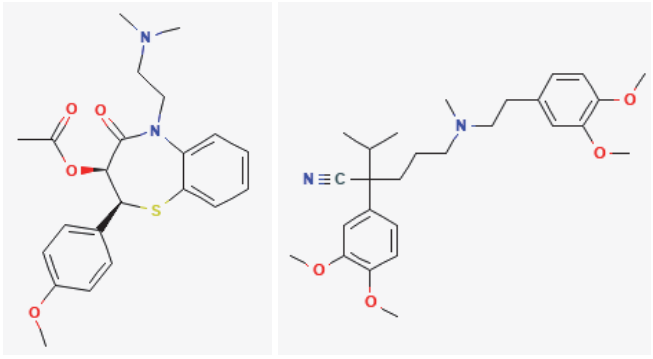

Fig. 5. Structure of diltiazem – **left** (https://pubchem.ncbi.nlm.nih.gov/compound/Diltiazem) and verapamil – **right** (https://pubchem.ncbi.nlm.nih.gov/compound/Verapamil)

Steinkey et al. (2019) studied the effect of diltiazem on *D. magna*. When exposed to environmentally relevant concentrations, increased heart rate and oxygen consumption were observed, though the exposure did not affect feeding behaviour or thoracic limb activity.

Steinbach et al. (2016) tested the influence of diltiazem on rainbow trout (*Oncorhynchus mykiss*); they found that exposure to the environmentally relevant concentrations of 30 ng/l led to the altered activity of some enzymes, namely antioxidant enzymes in the liver and gills. Also, a transient elevation of lipid oxidation measured as an increase in TBARS level (thiobarbituric acid reactive substances) in the gills was observed.

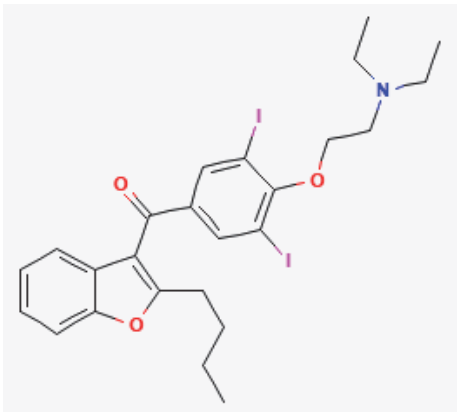

Fig. 6. Structure of amiodarone (https://pubchem.ncbi.nlm.nih.gov/compound/Amiodarone)

Numerous studies have been carried out to get better insight into the adverse effects of verapamil on various aquatic organisms. Zhi-Hua et al. (2010, 2011) observed behavioural changes, tissue-specific antioxidant responses, changes in haematological parameters, and decreased RNA/DNA ratio in fish muscle tissue in juvenile rainbow trout (*Oncorhynchus mykiss*) in the acute toxicity test; all these effects intensified with increasing verapamil concentrations. Ajima et al. (2017a, b) exposed the Nile tilapia fish (*Orechromis niloticus*) to verapamil in both acute and long-term tests. Exposure to sublethal concentrations revealed multiple effects including, on the one hand, the inhibition of some enzymes such as oxidative enzymes (catalase, superoxide dismutase, and glutathione peroxidase) or acetylcholinesterase enzyme and, on the other hand, an increase in the activity of glutathione-S-transferase, an enzyme belonging to the family of detoxification enzymes protecting the cell from oxidative damage (Kumar and Trivedi, 2018). Exposure of the common carp (*Cyprinus carpio*) to verapamil reduced the heart rate in both embryos and larvae (Steinbach et al., 2013). No effects were observed in this study regarding condition factors, ontogeny, growth, hatching, or accumulated mortality of the fish. Nonetheless, concentrations as high as tens and hundreds of µg/l resulted in a higher occurrence of oedemas and/or malformations compared with the control group. Exposure of early life-stages of the fathead minnow (*Pimephales promelas*) to verapamil was studied by Overturf et al. (2012). The investigation revealed a notable decrease in growth when relatively high verapamil concentrations (600 µg/l) were applied. Minguez et al. (2016) surprisingly noticed deleterious effects of verapamil even on photosynthesising organisms – they observed a pronounced growth inhibition in the alga *Raphidocelis subcapitata*.

Amiodarone's adverse effects on aquatic organisms have been reported by several authors.

Shi et al. (2012) performed chronic toxicity tests with embryos and larvae of the amphibian *Xenopus tropicalis* to study the influence of the drug on early amphibian development. They found that the body length and biomass were notably decreased, and individual developmental stages were delayed in the presence of the drug.

Sanoh et al. (2020) observed suppression of thyroid hormone-controlled spontaneous metamorphosis in amphibians (*Xenopus laevis* and *Xenopus tropicalis*) caused by inhibition of the thyroid hormone receptor-mediated gene.

Santos et al. (2023) studied the effect of amiodarone on the embryo-larval stages of a zebrafish *Danio rerio*. Blood

coagulation and yolk sac oedema were observed at the embryo stage, while in the larval stage, the absence of the swim bladder was the most commonly observed malformation, followed by spine deformities.

Photo-Fenton decomposition (decomposition by H_2O_2 catalysed by Fe^{2+} formed by photochemical reduction of Fe^{3+} *in situ*) of the beta-blockers atenolol and metoprolol with subsequent toxicity tests on *Vibrio fischeri* of parent compounds and photodegradation intermediates was carried out by Veloutsou et al. (2014). Toxicity evaluation using this bacterium proved that metoprolol and its intermediates are only moderately toxic to the bacterium, while atenolol's intermediates showed higher toxicity than the parent compound. Četojević-Simin et al. (2013) performed a toxicity assessment of metoprolol and its photoproducts mixture obtained by photochemical degradation in the presence of TiO_2 as a heterogeneous catalyst on several mammalian cell lines; they found that photocatalysed degradation promoted a time-dependent increase in toxicity.

Photochemical transformation together with a toxicity test of photoproduct mixtures was recently investigated for verapamil by Klementová et al. (2020), and for amiodarone by Trawiński and Skibiński (2022).

Klementová et al. (2020) found that phototransformation of verapamil resulted in the formation of norverapamil and a series of twenty-one other minor products. Toxicity assays in sublethal concentrations did not show any direct negative response in *Daphnia magna* to verapamil but the mixture of photoproducts notably lowered both the number of clutches and the number of juveniles in individual clutches, as well as the body size of *Daphnia*. The exposure of *Daphnia* to norverapamil resulted in the same (only even more pronounced) effects as the exposure to photoproduct mixture. All this led to the conclusion that norverapamil was mainly responsible for the toxicity of the photoproduct mixture and that norverapamil produced either in the metabolic pathway of the parent drug in the human body or subsequently photochemically in sunlit waters might pose a notable threat to aquatic invertebrates.

Trawiński abd Skibiński (2022) investigated the phototransformation of amiodarone, as well as the toxicity of the parent drug and several of its identified photoproducts. They identified twelve photoproducts, the two most abundant of which proved to be over 100 times more toxic than amiodarone itself. One of these photoproducts also represents a metabolite of amiodarone in the human body which provides an analogy to the verapamil situation as an environmental threat.

Antibiotics

Antibiotics, compounds able to kill or inhibit the growth of microorganisms, are grouped into classes based on their chemical structure. However, antibiotics within each class may be effective against different organisms (Werth, 2022).

Based on data from 76 countries, the total global consumption of antibiotics grew by almost 40% between 2000 and 2015 to more than 40 billion defined daily doses (Klein et al., 2018).

As reported by Van Boeckel et al. (2014), the highest per capita human antibiotic consumption in 2010 was seen in India, China, and the US. For animal use, the highest antibiotic consumption (an estimated average of antibiotics for cattle, chicken, and pigs being 45 mg/kg, 148 mg/kg, and 172 mg/kg, respectively) occurred in southeast China, the Red River delta in Vietnam, the south coast of India and, the Midwestern and Southern states in the US (Van Boeckel et al., 2015).

Antibiotics are eliminated from both the human and animal body mainly through the renal and/or biliary system, either as an original unchanged parent compound or as a metabolite, or sometimes as conjugates of glucuronic acid (Tran et al., 2018). Even though individual antibiotics vary widely in the degree to which they are metabolised before excretion, Dinh et al. (2017) evaluated that approximately 75% of antibiotics enter sewage systems in unchanged forms.

The mean concentrations of eight selected antibiotics (amoxicillin, ciprofloxacin, erythromycin, ofloxacin, oxytetracycline, sulfamethoxazole, tetracycline, trimethoprim) in Asia and Europe are summarised in the review of Kovalakova et al. (2020). In Europe, the concentrations ranged from tens to hundreds of ng/l; in Asia, they reached μg/l (tetracycline, ofloxacin), tens of μg/l (oxytetracycline), and even hundreds of μg/l (ciprofloxacin). The structures of the antibiotics are depicted in Fig. 7 (amoxicillin), Fig. 8 (ciprofloxacin, ofloxacin), Fig. 9 (erythromycin), Fig. 10 (tetracycline, oxytetracycline), and Fig. 11 (sulfamethoxazole and trimethoprim).

The toxicity of antibiotics to non-target organisms has been studied by many scientists with the aim of gaining a better insight into the ecosystem effects of antibiotics. Kovalakova et al. (2020) summarised the ecotoxicity of the eight selected antibiotics (see above) as assessed in multiple independent studies. Cyanobacteria were observed to be extremely sensitive to some antibiotics (amoxicillin, ciprofloxacin, ofloxacin), with EC_{50} (half maximal effective concentrations) values

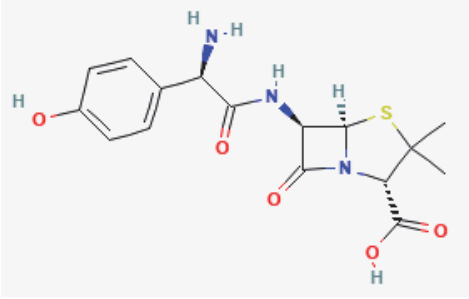

Fig. 7. Structure of penicillin (https://pubchem.ncbi.nlm.nih.gov/compound/Penicillin)

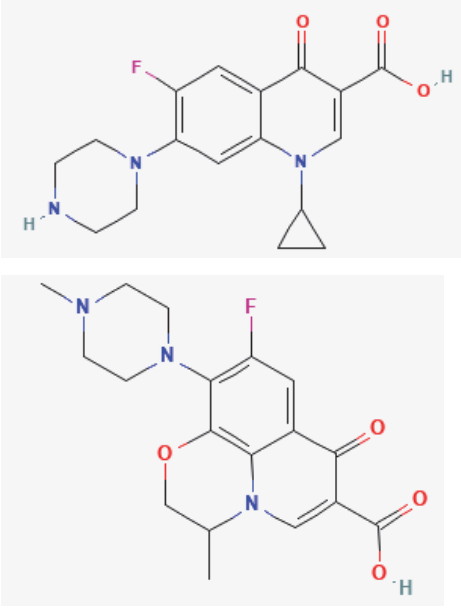

Fig. 8. Structure of ciprofloxacin – **up** (https://pubchem.ncbi.nlm.nih.gov/compound/Ciprofloxacin) and ofloxacin – **down** (https://pubchem.ncbi.nlm.nih.gov/compound/Ofloxacin)

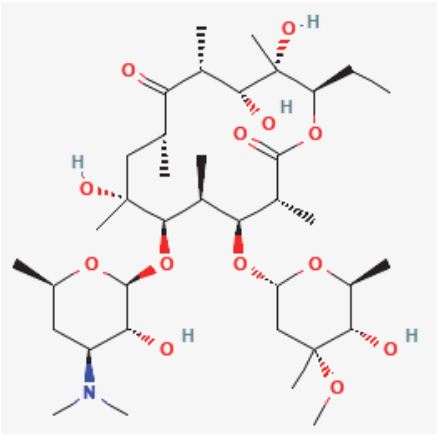

Fig. 9. Structure of erythromycin (https://pubchem.ncbi.nlm.nih.gov/compound/Erythromycin)

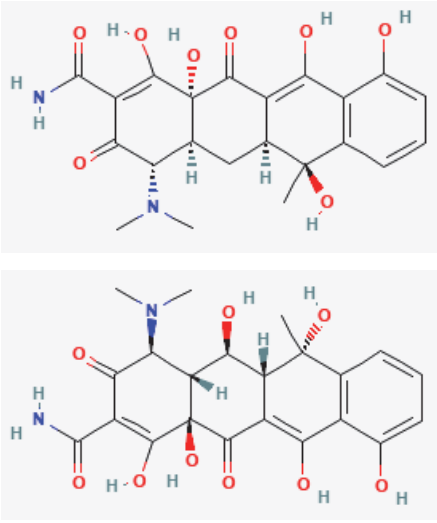

Fig. 10. Structure of tetracycline – **up** (https://pubchem.ncbi.nlm.nih.gov/compound/Tetracycline) and oxytetracycline – **down** (https://pubchem.ncbi.nlm.nih.gov/compound/Biostat)

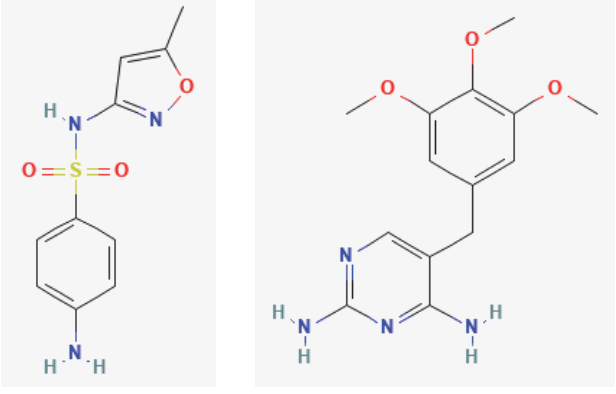

Fig. 11. Structure of sulfamethoxazole – **left** (https://pubchem.ncbi.nlm.nih.gov/compound/Sulfamethoxazole) and trimethoprim – **right** (https://pubchem.ncbi.nlm.nih.gov/compound/Trimethoprim)

being in tens of μg/l. Algae and plants had EC_{50} values one order of magnitude higher, and crustaceans and fish EC_{50} values reached approximately hundreds of mg/l.

In the study by Yuan et al. (2011), antibiotics oxytetracycline, doxycycline, and ciprofloxacin were degraded by irradiation of a low-pressure mercury lamp either with or without added H_2O_2 with subsequent tests of toxicity on *Vibrio fischeri*. UV treatment alone increased assessed toxicity, while in the UV/H_2O_2 process, toxicity increased in the initial stages of the reaction, and subsequently declined, which – according to the authors – might be the consequence of the gradual complete mineralisation of the organic substances in the oxidative environment.

Sturini et al. (2015) investigated the photochemical degradation of five fluoroquinolone antibiotics (ciprofloxacin, danofloxacin, enrofloxacin, levofloxacin, and marbofloxacin) under solar light, again with a subsequent toxicity test on *Vibrio fischeri*. Their results conclusively showed that irradiation under this condition is an important removal pathway for these otherwise persistent contaminants in surface waters and that the observed toxic effect was due to photodegradation products.

Klementová et al. (2022) investigated the photochemical degradation of three fluoroquinolones (ciprofloxacin, enrofloxacin, and norfloxacin) under light conditions imitating the shortest-wavelength solar radiation. Besides providing a comprehensive photoproduct identification, the authors performed toxicity tests on *Escherichia coli* and *Staphylococcus epidermidis*. They found that the photodegradation mechanism is strongly dependent on pH, with significantly more complex reaction schemes occurring at alkaline pH compared with neutral pH. Norfloxacin photoproducts did not exhibit antibacterial activity. On the other hand, photoproducts of ciprofloxacin and enrofloxacin showed extremely enhanced antibacterial activities compared to their parent compounds.

Antibiotics in aquatic systems are considered to pose a threat to public health since they might significantly contribute to the evolution of resistant species (Carvalho and Santos, 2016; Kusi et al., 2022). Antibiotic residues including products of their natural photochemical transformation with increased antibacterial activity might enhance these adverse effects.

Conclusion

In all presented groups of the most widely used pharmaceuticals, the adverse effects of products of photoinitiated degradation on organisms of the aquatic ecosystem were reported.

Such findings accentuate the need to contemplate not only the parental drugs when assessing environmental risks, but also the possibility of the generation of toxicologically relevant photochemically induced degradation products.

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Ethical aspects and conflict of interest
The authors have no conflict of interest to declare.

References

Ajima MNO, Pandey PK, Kumar K, Poojary N (2017a). Neurotoxic effects, molecular responses and oxidative stress biomarkers in Nile tilapia, *Oreochromis niloticus* (Linneaus, 1758). Comp Biochem Physiol C Toxicol Pharmacol 196: 44–52. DOI: 10.1016/j.cbpc.2017.03.009.

Ajima MNO, Pandey PK, Kumar K, Poojary N (2017b). Assessment of mutagenic, hematological and oxidative stress biomarkers in liver of Nile tilapia, *Oreochromis niloticus* (Linnaeus, 1758) in response to sublethal verapamil exposure. Drug Chem Toxicol 40: 286–294. DOI: 10.1080/01480545.2016.1219914.

Allouche M, Ishak S, Ben Ali M, Hedfi A, Almalku M, Karachle PK, et al. (2022). Molecular interactions of polyvinylchloride microplastics and beta-blockers (diltiazem and bisoprolol) and their effects on marine meiofauna: Combined *in vivo* and modeling study. J Hazard Mater 431: 128609. DOI: 10.1016/j.jhazmat.2022.128609.

Alonso SG, Catalá M, Maroto RR, Gil JLR, de Miguel ÁG, Valcárcel Y (2010). Pollution by psychoactive pharmaceuticals in the rivers of Madrid metropolitan area (Spain). Environ Int 36: 195–201. DOI: 10.1016/j.envint.2009.11.004.

Ambrosio-Albuquerque EP, Cusioli LF, Bergamasco R, Gigliolli AAS, Lupepsa L, Paupitz BR, et al. (2021). Metformin environmental exposure: A systematic review. Environ Toxicol Pharmacol 83: 103588. DOI: 10.1016/j.etap.2021.103588.

Aus der Beek T, Weber FA, Bergmann A, Hickmann S, Ebert I, Hein A, Küster A (2016). Pharmaceutical in the environment – global occurrences and perspectives. Environ Toxicol Chem 35: 823–835. DOI: 10.1002/etc.3339.

Bailey CJ (2017). Metformin: historical overview. Diabetologia 60: 1566–1576. DOI: 10.1007/s00125-017-4318-z.

Barton AK, McGowan M, Smyth A, Wright GA, Gardner RS (2020). Classification and choice of antiarrhythmic therapies. Prescriber, Wiley Online Library, pp. 11–17. DOI: 10.1002/psb.1828.

Batt AL, Kincaid TM, Kostich MS, Latorchak JM, Olsen AR (2015). Evaluating the extent of pharmaceuticals in surface waters of the United States using a national-scale rivers and streams assessment survey. Environ Toxicol Chem 35: 874–881. DOI: 10.1002/etc.3161.

Boreen AL, Arnold WA, McNeill K (2003). Photodegradation of pharmaceutical in the aquatic environment: A review. Aquatic Sci 65: 320–341. DOI: 10.1007/s00027-003-0672-7.

Briones R, Sarmah A, Padhye LP (2016). A global perspective on the use, occurrence, fate and effects of anti-diabetic drg metformin in natural and engineered ecosystems. Environ Pollut 219: 1007–1020. DOI: 10.1016/j.envpol.2016.07.040.

Brocker CN, Velenose T, Flaten HK, McWilliams G, McDaniel K, Shelton SK, et al. (2020). Metabolomic profiling of metoprolol hypertension treatment reveals altered gut microbiota-derived urinary metabolites Hum Genomics 14: 10. DOI: 10.1186/s40246-020-00260-w.

Calza P, Jiménez-Hogado C, Coha M, Chrimatopoulos C, Dal Bello F, Medana C, Sakkas V (2021). Study of the photoinduced transformation of sertraline in aqueous media. Sci Total Environ 756: 143805. DOI: 10.1016/j.scitotenv.2020.143805.

Carvalho IT, Santos L (2016). Antibiotics in the aquatic environments: A review of the European scenario. Environ Int 94: 736–757. DOI: 10.1016/j.envint.2016.06.025.

Četojević-Simin DD, Armaković SJ, Šojić DV, Abramović BF (2013). Toxicity assessment of metoprolol and its photodegradation mixtures obtained by using different type of TiO_2 catalysts in the mammalian cell lines. Sci Total Environ 463–464: 968–974. DOI: 10.1016/j.scitotenv.2013.06.083.

Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti A, Chada A, Ravilla R, et al. (2017). Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management. Front Endocrinol (Lausanne) 8: 6. DOI: 10.3389/fendo.2017.00006.

ClinCalc (2021a). ClinCalc DrugStats Database, Free U.S. outpatient usage statistics. [online] [cit. 2023-01-22]. Available from: https://clincalc.com/DrugStats/

ClinCalc (2021b). Sertraline – Drug Usage Statistics, US 2013–2020. [online] [cit. 2023-01-22]. Available from: https://clincalc.com/DrugStats/Drugs/Sertraline

ClinCalc (2021c). Fluoxetine – Drug Usage Statistics, US 2013–2020. [online] [cit. 2023-01-22]. Available from: https://clincalc.com/DrugStats/Drugs/Fluoxetine

ClinCalc (2022). The top 200 of 2020. [online] [cit. 2023-01-22]. Available from: https://clincalc.com/DrugStats/Top200Drugs.aspx

ClinCalc (2023). Metformin – Drug Usage Statistics, US 2013–2020. [online] [cit. 2023-01-22]. Available from: https://clincalc.com/DrugStats/Drugs/Metformin

Conley JM, Symes SJ, Kindelberger SA, Richards SM (2008). Rapid liquid chromatography-tandem mass spectrometry method for the determination of a broad mixture of pharmaceuticals in surface water. J Chromatogr A 1185: 206–215. DOI: 10.1016/j.chroma.2008.01.064.

Dahlén AD, Dashi G, Maslov I, Attwood MM, Jonsson J, Trukhan V, Schiöth HB (2022). Trends in antidiabetic drug discovery: FDA approved drugs, new drugs in clinical trials and global sales. Front Pharmacol 12: 807548. DOI: 10.3389/fphar.2021.807548.

de Barros ALC, Schmidt FF, de Aquino SF, De Cássia Franco Afonso RJCF (2018). Determination of nine pharmaceutical active compounds in surface waters from Paraopeba River Basin in Brazil by LTPE-HPLC-ESI-MS/MS. Environ Sci Pollut Res Int 25: 19962–19974. DOI: 10.1007/s11356-018-2123-y.

De Farias O, Oliveira R, Sousa-Moura E, De Oliveira RCS, Carvalho Rodrigues MA, Sousa Andrade T, et al. (2019). Exposure to low concentration of fluoxetine affects development, behaviour and acetylcholinesterase activity of zebrafish embryos. Comp Biochem Physiol Part C Toxicol Pharmacol 215: 1–8. DOI: 10.1016/j.cbpc.2018.08.009.

Dinh QT, Moreau-Guigon E, Labadie P, Alliot F, Teil MJ, Blanchard M, Chevreuil M (2017). Occurrence of antibiotics in rural catchment. Chemosphere 168: 483–490. DOI: 10.1016/j.chemosphere.2016.10.106.

Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar Ya, et al. (2021). Selective serotonin reuptake inhibitors and adverse effects: A narrative review. Neurol Inf 13: 387–401. DOI: 10.3390/neurolint13030038.

Elizalde-Velázquez GA, Gómez-Oliván LM, García-Medina S, Islas-Flores H, Hernánez-Navarro MD, Galar-Martínez M (2021). Antidiabetic drug metformin disrupts the embryogenesis in zebrafish through an oxidative stress mechanism. Chemosphere 285: 131213. DOI: 10.1016/j.chemosphere.2021.131213.

Fact Sheet (2021). Fact Sheet: FDA at a glance. [online] [cit. 2023-01-22]. Available from: https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance

Falfushynska H, Sokolov EP, Haider F, Oppeermann C, Kragl U, Ruth W, et al. (2019). Effects of a common pharmaceutical, atorvastatin, on energy metabolism and detoxification mechanisms of a marine bivalve *Mytilus edulis*. Aquat Toxicol 208: 47–61. DOI: 10.1016/j.aquatox.2018.12.022.

Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE (2012). Metformin pathways: pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics 22: 820–827. DOI: 10.1097/FPC.0b013e3283559b22.

Godoy AA, Domingues I, Arsénia Nogueira AJ, Kummrow F (2018). Ecotoxicological effects, water quality standards and risk assessment for the anti-diabetic metformin. Environ Pollut 243(Pt A): 534–542. DOI: 10.1016/j.envpol.2018.09.031.

Gwenzi W, Selvasembian R, Offiong NAO, Mahmoud AED, Sanganyado E, Mal J (2022). COVID-19 drugs in aquatic systems: a review. Environ Chem Lett 20: 1275–1294. DOI: 10.1007/s10311-021-01356-y.

Harrison TJ, Chen X, Yasoshima K, Bauer D (2023). Phototoxicity – medicinal chemistry strageties for risk mitigation in drug discovery. J Med Chem 66: 9345–9362. DOI: 10.1021/acs.jmedchem.3c00749.

Hu L, Ding R, Nie X (2022): Comparison of toxic effects of atorvastatin and gemfibrozil on *Daphnia magna*. Compa Biochem Physiol C Toxicol Pharmacol 252: 109224. DOI: 10.1016/j.cbpc.2021.109224.

Iancu VI, Puiu D, Radu GL (2020). Determination of some beta-blockers in surface water samples. UPB Sci Bull, Series B 82. [online] [cit. 2023-01-22]. Available from: https://www.researchgate.net/publication/342201065_DETERMINATION_OF_SOME_BETA-BLOCKERS_IN_SURFACE_WATER_SAMPLES

Jacob S, Knoll S, Huhn C, Köhler H-R, Tisler S, Zwiener C, Triebskorn R (2019). Effects of guanylurea, the transformation product of the antidiabetic drug metformin, on the health of brown trout (*Salmo trutta* f. *fario*). Peer J 7: e7289. DOI: 10.7717/peerj.7289.

Khasawneh OFS, Palaniandy P (2021). Occurrence and removal of pharmaceuticals in wastewater treatment plants. Process Safety Environ Protection 150: 532–556. DOI: 10.1016/j.psep.2021.04.045.

Khetan SK, Collins TJ (2007). Human pharmaceuticals in the aquatic environment: A challenge to green chemistry. Chem Rev 107: 2319–2364. DOI: 10.1021/cr020441w.

Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. (2018). Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proceed Nat Acad Sci USA 115: E3463–E3470. DOI: 10.1073/pnas.1717295115.

Klelemen H, Hancu G, Kascó E, Papp LA (2022). Photosensitivity reactions induced by photochemical degradation of drugs. Adv Pharm Bull 12: 77–85. DOI: 10.34172/apb.2022.010.

Klementová Š, Hornychová L, Šorf M, Zemanová J, Kahoun D (2019). Toxicity of atrazine and the products of its homogeneous photocatalytic degradation on the aquatic organisms *Lemna minor* and *Daphnia magna*. Environ Sci Pollut Res 26: 27259–27267. DOI: 10.1007/s11356-019-05710-0.

Klementová Š, Kahoun D, Doubková L, Frejlachová K, Dušáková M, Zlámal M (2017). Catalytic photodegradation of pharmaceuticals – homogeneous and heterogeneous photocatalysis. Photochem Photobiol Sci 16: 67–71. DOI: 10.1039/c6pp00164e.

Klementová Š, Petráňová P, Fojtíková P (2021). Photodegradation of atorvastatin under light conditions relevant to natural waters and photoproducts toxicity assessment. Open J Appl Sci 11: 489–499. DOI: 10.4236/ojapps.2021.104035.

Klementová Š, Poncarová M, Kahoun D, Šorf M, Dokoupilová E, Fojtíková P (2020). Toxicity assessment of verapamil and its photodegradation products. Environ Sci Pollut Res 27: 35650–35660. DOI: 10.1007/s11356-020-09830-w.

Klementová Š, Poncarová M, Langhansová H, Lieskovská J, Kahoun D, Fojtíková P (2022). Photodegradation of fluoroquinolones in aqueous solution under light conditions relevant to surface waters, toxicity assessment of photoproduct mixtures. Environ Sci Pollut Res 29: 13941–13962. DOI :10.1007/s11356-021-16182-6.

Komesli OT, Muz M, Ak MS, Bakirdere S, Gokcay CF (2015). Occurrence, fate and removal of endocrine disrupting compounds (IDCs) in Turkish wastewater treatment plants. Chem Eng J 277: 202–208. DOI: 10.1016/j.cej.2015.04.115.

Kostich MS, Batt AL, Lazorchak JM (2014). Concentrations of prioritized pharmaceuticals in effluents from 50 large wastewater treatment plants in the US and implications for risk estimation. Environ Pollut 184: 354–359. DOI: 10.1016/j.envpol.2013.09.013.

Kovalakova P, Cizmas L, McDonald TJ, Marsalek B, Feng M, Sharma VK (2020). Occurrence and toxicity of antibiotics in the aquatic environment. A review. Chemosphere 251: 126351. DOI: 10.1016/j.chemosphere.2020.126351.

Kumar S, Trivedi PK (2018). Glutathione S-transferases: Role in Combating abiotic stresses including arsenic detoxification in plants. Front Plant Sci 9: 751. DOI: 10.3389/fpls.2018.00751.

Kusi J, Ojewole CO, Ojewole AE, Nwi-Mozu I (2022). Antimicrobial Resistance Development Pathways in Surface Waters and Publick Health Implications. Antibiotics (Basel) 11: 821. DOI: 10.3390/antibiotics11060821.

Lajeunesse A, Smyth SA, Barclay K, Sauve S, Gagnon C (2012). Distribution of antidepressant residues in wastewater and biosolids following different treatment processes by municipal wastewater treatment plants in Canada. Water Res 46: 5600–5612. DOI: 10.1016/j.watres.2012.07.042.

Lalji HM, McGrogan A, Bailey SJ (2021). An analysis of antidepressant prescribing trends in England 2015–2019. J Affect Disord Rep 6: 100205. DOI: 10.1016/j.jadr.2021.100205.

Latini R, Tognoni G, Kates RE (1984). Clinical pharmacokinetics of amiodarone. Clin Pharmacokinet 9: 136–156. DOI: 10.2165/00003088-198409020-00002.

Lee HB, Peart TE, Svoboda ML, Backus S (2009). Occurrence and fate of rosuvastatin, rosuvastatin lactone, and atorvastatin in Canadian sewage and surface water samples. Chemosphere 77: 1285–1291. DOI: 10.1016/j.chemosphere.2009.09.068.

Li WC (2014). Occurrence, sources, and fate of pharmaceuticals in aquatic environment and soil. Environ Pollut 187: 193–201. DOI: 10.1016/j.envpol.2014.01.015.

Mayo Clinic (2023). Type 1 diabetes, diagnosis and treatment. [online] [cit. 2023-01-22]. Available from: https://www.mayoclinic.org/diseases-conditions/type-1-diabetes/diagnosis-treatment/drc-20353017

Mezzelani M, Gorbi S, Regoli F (2018). Pharmaceutical in the aquatic environments: Evidence of emerged threat and future challenges for marine organisms. Mar Environ Res 140: 41–60. DOI: 10.1016/j.marenvres.2018.05.001.

Minguez L, Pedelucq J, Farcy E, Ballandonne C, Budzinski H, Halm-Lemeille MP (2016). Toxicities of 48 pharmaceuticals and their freshwater and marine environmental assessment in northwestern France. Environ Sci Pollut Res 23: 4992–5001. DOI: 10.1007/s11356-014-3662-5.

Ministry of Agriculture of the Czech Republic (2019). Zpráva o stavu vodního hospodářství České republiky v roce 2018. [online] [cit. 2023-01-22]. Available from: https://eagri.cz/public/portal/mze/voda/osveta-a-publikace/publikace-a-dokumenty/modre-zpravy/zprava-o-stavu-vodniho-hosp-2018.html

NHS (2021). Overview – Antidepressants. [online] [cit. 2023-01-22]. Available from: https://www.nhs.uk/mental-health/talking-therapies-medicine-treatments/medicines-and-psychiatry/antidepressants/overview/

OECD 201 (2011). OECD guidelines for testing of chemicals. Test No. 201: Freshwater alga and cyanobacteria, growth inhibition test. [online] [cit. 2023-01-22]. Available from: https://www.oecd-ilibrary.org/environment/test-no-201-alga-growth-inhibition-test_9789264069923-en

OECD 202 (2004). OECD guidelines for testing of chemicals. Test No. 202: *Daphnia* sp. acute immobilisation test. [online] [cit. 2023-01-22]. Available from: https://read.oecd-ilibrary.org/environment/test-no-202-daphnia-sp-acute-immobilisation-test_9789264069947-en#page1

OECD 203 (2019). OECD guidelines for testing of chemicals. Test No. 203: Fish, acute toxicity test. [online] [cit. 2023-01-22]. Available from: https://www.oecd-ilibrary.org/environment/test-no-203-fish-acute-toxicity-test_9789264069961-en

OECD 211 (2012). OECD guidelines for testing of chemicals. Test No. 211: *Daphnia magna* reproduction test. [online] [cit. 2023-01-22]. Available from: https://www.oecd.org/chemicalsafety/test-no-211-daphnia-magna-reproduction-test-9789264185203-en.htm

OECD 221 (2006). OECD guidelines for testing of chemicals. Test No. 221: *Lemna* sp. growth inhibition test. [online] [cit. 2023-01-22]. Available from: https://www.oecd-ilibrary.org/environment/test-no-221-lemna-sp-growth-inhabition-test_9789264016194-en

Ofoegbu PU, Lourenco J, Mendo S, Soares AMVM, Pestana JLT (2019). Effects of low concentration of psychiatric drugs (carbamazepine and fluoxetine) on the freshwater planarian, *Schmidtea mediterranea*. Chemosphere 217: 542–549. DOI: 10.1016/j.chemosphere.2018.10.198.

Overturf MD, Overturf CL, Baxter D, Hala DN, Constantine L, Venables B, Huggett DB (2012). Early life-stage toxicity of eight pharmaceuticals to the fathead minnow, *Pimephales promelas*. Arch Environ Contam Toxicol 62: 455–464. DOI: 10.1007/s00244-011-9723-6.

Pahan K (2006). Lipid-lowering drugs. Cell Mol Life Sci 63: 1165–1178. DOI: 10.1007/s00018-005-5406-7.

Pan C, Zhu F, Wu M, Jiang L, Zhao X, Yang M (2022). Degradation and toxicity of the antidepressant fluoxetine in an aqueous system

by UV irradiation. Chemosphere 287: 132434. DOI: 10.1016/j.chemosphere.2021.132434.

Patel M, Kumar R, Kishor K, Mlsna T, Pittman CU, Jr., Mohan D (2019). Pharmaceuticals of emerging concern in aquatic systems: Chemistry, occurrence, effects, and removal methods. Chem Rev 119: 3510–3673. DOI: 10.1021/acs.chemrev.8b00299.

Ribeiro S, Torres T, Martins R, Santos MM (2015). Toxicity screening of diclofenac, propranolol, sertraline and simvastatin using *Danio rerio* and *Paracentrotus lividus* embryo bioassays. Ecotox Environ Saf 114: 67–74. DOI: 10.1016/j.ecoenv.2015.01.008.

Sanoh S, Hanada H, Kashiwagi K, Mori T, Goto-Inoue N, Suzuki KT, et al. (2020). Amiodarone bioconcentration and suppression of metamorphosis in *Xenopus*. Aquat Toxicol 228: 105623. DOI: 10.1016/j.aquatox.2020.105623.

Santarsieri D, Schwartz TL (2015). Antidepressant efficacy and side-effect burden: A quick guide for clinicans. Drugs Context 4: 212290. DOI: 10.7573/dic.212290.

Santos LHMLM, Araújo AN, Fachini A, Pena A, Delerue-Matos C, Montenegro MCBSM (2010). Ecotoxicological aspect related to the presence of pharmaceuticals in the aquatic environment. J. Hazard Mater 175: 45–95. DOI: 10.1016/j.jhazmat.2009.10.100.

Santos LHMLM, Gros M, Mozaz SR, Matos CD, Pena A, Barceló D, Montenegro MCBSM (2013). Contribution of hospital effluents to the load of pharmaceuticals in urban wastewater: identification of ecologically relevant pharmaceutical. Sci Total Environ 461–462: 302–316. DOI: 10.1016/j.scitotenv.2013.04.077.

Santos TP, Da Silva Bastos PE, Da Sila JF, De Medeiros Vieira SM, Da Silva MCG, De Andrade ALC, et al. (2023). Single and joint toxic effects of thyroid hormone, levothyroxine, and amiodarone on embryo-larval stages of zebrafish (*Danio rerio*). Ecotoxicol 32: 525–535. DOI: 10.1007/s10646-023-02655-6.

Sebastine IM, Wakeman RJ (2003). Consumption and environmental hazards of pharmaceutical substances in the UK. Process Saf Environ Prot 81: 229–235. DOI: 10.1205/095758203322299743.

Shi H, Sun Z, Liu Z, Xue Y (2012). Effects of clotrimazole and amiodarone on early development of amphibian (*Xenopus tropicalis*). Toxicol Environ Chem 94: 128–135. DOI: 10.1080/02772248.2011.634643.

Stancu C, Sima A (2001). Statins: mechanism of action and effects. Cell Mol Med 5: 378–387. DOI: 10.1111/j.1582-4934.2001.tb00172.x.

Steinbach C, Burkina V, Schmidt H (2016). Effect of the human therapeutic drug diltiazem on the haematological parameters, histology and selected enzymatic activities of rainbow trout *Oncorhynchus mykiss*. Chemosphere 157: 57–64. DOI: 10.1016/j.chemosphere.2016.04.137.

Steinbach C, Fedorova G, Prokes M, Grabicova K, Machova J, Grabic R, et al. (2013). Toxic effects, bioconcentration and depuration of verapamil in the early life stages of common carp (*Cyprinus carpio* L.). Sci Total Environ 461–462: 198–206. DOI: 10.1016/j.scitotenv.2013.05.002.

Steinkey D, Lari E, Woodman SG, Steinkey R, Luong KH, Wong CS, Pyle GG (2019). The effects of diltiazem on growth, reproduction, energy reserves, and calcium-dependent physiology in *Daphna magna*. Chemosphere 232: 424–429. DOI: 10.1016/j.chemosphere.2019.05.176.

Stöppler MC (2023). Definition of antidepressant. RxList. [online] [cit. 2023-01-22]. Available from: https://www.rxlist.com/antidepressants/definition.htm

Sturini M, Speltini A, Maraschi F, Pretali L, Ferri EN, Profumo A (2015). Sunlight-induced degradation of fluoroquinolones in wastewater effluent: Photoproducts identification and toxicity. Chemosphere 134: 313–318. DOI: 10.1016/j.chemosphere.2015.04.081.

Taljera O, Cassagnol M (2022). Diltiazem. Nat. Center for Biotechnol Inf., Statpearls Publishing. [online] [cit. 2023-01-22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532937/

Tete VS, Nyoni H, Mamba BB, Msagati TAM (2020). Occurrence and spatial distribution of statins, fibrates and their metabolites in aquatic environments. Arab J Chem 13: 4358–4373. DOI: 10.1016/j.arabjc.2019.08.003.

Tixier C, Sancelme M, Ait-Aissa S, Gadona-Widehem P (2002). Biotransformation of phenylurea herbicides by a soil bacterial strain, *Arthrobacter* sp. N2: Structure, ecotoxicity and fate of diuron metabolite with soil fungi. Chemosphere 46: 519–526. DOI: 10.1016/S0045-6535(01)00193-X.

Tixier C, Sancelme M, Bonnemoy F, Cuer A, Veschambre H (2009). Degradation products of a phenylurea herbicide, diuron. Synthesis, ecotoxicity, and biotransformation. Environ Toxicol Chem 20: 1381–1389. DOI: 10.1002/etc.5620200701.

Tran NH, Reinhard M, Gin KYH (2018). Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions – a review. Water Res 133: 182–207. DOI: 10.1016/j.watres.2017.12.029.

Trautwein C, Kümmerer K (2011). Incomplete aerobic degradation of the antidiabetic drug metformin and identification of the bacterial dead-end transformation product guanylurea. Chemospere 85: 765–773. DOI: 10.1016/j.chemosphere.2011.06.057.

Trawiński J, Skibiński R (2022). Comparative analysis of *in vivo* and *in silico* toxicity evaluation of the organoiodine compounds towards *D. magna* using multivariate chemometric approach: A study on the example of amiodarone phototransformation products. Chemosphere 292: 133420. DOI: 10.1016/j.chemosphere.2021.133420.

Ussery E, Nielsen KM, Pandelides Z, Kirkwood AE, Guchardi J, Holdway D (2019). Developmental and full-life cycle exposures to guanylurea and guanylurea-metformin mixtures result in adverse effects on Japanese Medaka (*Oryzias latipes*). Environ Toxicol Chem 38: 1023–1028. DOI: 10.1002/etc.4403.

Van Boeckel TP, Brower C, Gilbert M, Laxminarayan R (2015). Global trends in antimicrobial use in food animals. PNAS 112: 5649–5654. DOI: 10.1073/pnas.150314111.

Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, Laxminarayan R (2014). Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 14: 742–750. DOI: 10.1016/S1473-3099(14)70780-7.

Veloutsou S, Bizani E, Fytianos K (2014). Photo-Fenton decomposition of β-blockers atenolol and metoprolol; study and optimization of system parameters and identification of intermediates. Chemosphere 107: 180–186. DOI: 10.1016/j.chemosphere.2013.12.031.

Wei Z, Wei Y, Li H, Shi D, Yang D, Yin J (2022). Emerging pollutant metformin in water promotes the development of multiple-antibiotic resistance in *Escherichia coli* via chromosome mutagenesis. J Hazard Mater. 430: 128474. DOI: 10.1016/j.jhazmat.2022.128474.

Werth BJ (2022). Overview of antibiotics. MSD Manual. [online] [cit. 2023-01-22]. Available from: https://www.msdmanuals.com/home/infections/antibiotics/overview-of-antibiotics

Wilkinson JL, Boxall ABA, Kolpin DW, Leung KMY Lai RWS, Galbán-Malagón C, et al. (2022). Pharmaceutical pollution of the world's rivers. Prot Natl Acad Sci USA 119: e2113947119. DOI: 10.1073/pnas.2113947119.

Wu M, Xiang J, Que C, Chen F, Xu G (2015). Occurrence and fate of psychiatric pharmaceuticals in the urban water system of Shanghai, China. Chemosphere 138: 486–493. DOI: 10.1016/j.chemosphere.2015.07.002.

Yan JH, Xiao Y, Tan DQ, Shao XT, Wang Z, Wang DG (2019). Wastewater analysis reveals spatial pattern in consumption of anti-diabetes drug metformin in China. Chemosphere 222: 688–695. DOI: 10.1016/j.chemosphere.2019.01.151.

Yang Z, Lu T, Zhu Y, Zhang Q, Zhou Z, Pan X, Qian H (2019). Aquatic ecotoxicity of an antidepressant, sertraline hydrochloride, on microbial communities. Sci Total Environ 654: 129–134. DOI: 10.1016/j.scitotenv.2018.11.164.

Ying Han, Yuanyuan Ma, Junwei Tong, Jingpu Zha (2022). Systems assessment of statins hazard: Integrating *in silico* prediction, developmental toxicity profile and transcriptomics in zebafish. Ecotoxicol Environ Saf 243: 113981. DOI: 10.1016/j.ecoenv.2022.113981.

Yuan F, Hu C, Hu X, Wei D, Chen Y, Qu J (2011). Photodegradation and toxicity changes of antibiotics in UV and UV/H_2O_2

process. J Hazard Mater 185: 1256–1263. DOI: 10.1016/j.jhazmat.2010.10.040.

Yuan SL, Jiang XM, Xia XH, Zhang HX, Zheng SK (2013). Detection, occurrence and fate of 22 psychiatric pharmaceuticals in psychiatric hospital and municipal wastewater treatment plants in Beijing, China. Chemosphere 90: 2520–2525. DOI: 10.1016/j.chemosphere.2012.10.089.

Zhi-Hua L, Ping L, Randak T (2010). Ecotoxicological effects of short-term exposure to a human pharmaceutical verapamil in juvenile rainbow trout (*Oncorhynchus mykiss*). Comp Biochem Phys C Toxicol Pharmacol 152: 385–391. DOI: 10.1016/j.cbpc.2010.06.007.

Zhi-Hua L, Velisek J, Zlabek V, Grabic R, Machova J, Kolarova J, Ping L, Randak T (2011). Chronic toxicity of verapamil on juvenile rainbow trout (*Onkorhynchus mykiss*): effects on morphological indices, hematological parameters and antioxidant responses. J Hazard Mater 185: 870–880. DOI: 10.1016/j.jhazmat.2010.09.102.