Scilight

Earth: Environmental Sustainability
https://www.sciltp.com/journals/eesus

Review

Beyond Humans: Effects and Consequences of Illicit Drugs in the Aquatic Environment

Cristiana Roberta Multisanti [1], Serafina Ferrara [2], Giuseppe Stracuzzi [2], Damià Barceló [3], Giuseppe Piccione [1], Nima Shiry [4], Federica Impellitteri [1] and Caterina Faggio [2,5,*]

[1] Department of Veterinary Sciences, University of Messina, Viale Giovanni Palatucci snc, 98168 Messina, Italy
[2] Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Viale Ferdinando d'Alcontres, 31, 98166 Messina, Italy
[3] Chemistry and Physics Department, University of Almeria, 04120 Almeria, Spain
[4] Persian Gulf and Oman Sea Ecological Research Center, Iranian Fisheries Science Research Institute, Bandar Abbas 1417614411, Iran
[5] Department of Eco-Sustainable Marine Biotechnology, Stazione Zoologica Anton Dohrn, 80122 Naples, Italy
* Correspondence: cfaggio@unime.it

How To Cite: Multisanti, C.R.; Ferrara, S.; Stracuzzi, G.; et al. Beyond Humans: Effects and Consequences of Illicit Drugs in the Aquatic Environment. *Earth: Environmental Sustainability* **2026**, *2*(2), 231–249. https://doi.org/10.53941/eesus.2026.100016

Received: 8 January 2026
Revised: 14 April 2026
Accepted: 17 April 2026
Published: 9 June 2026

Abstract: The use of illicit drugs is one of the most serious problems today, both from a social and environmental point of view. After cannabis, one of the most widely used drugs is cocaine. Global cocaine abuse has led the scientific community to include it among emerging contaminants, as it has been detected in increasing quantities in various environmental matrices. In particular, numerous studies have detected the presence of cocaine in aquatic environments, with concentrations ranging from 0.13 ng L^{-1} to 537 ng L^{-1}, highlighting the potential implications for the organisms inhabiting these ecosystems. The consequences of exposure on the main inhabitants of the seawater and freshwater ecosystems, such as shellfish, crustaceans, and fish, are primarily attributable to physiological, biochemical, and behavioural alterations. These changes manifest as oxidative stress and neurotoxicity, which can lead to impaired growth, reproduction, and even survival of organisms. Furthermore, the ability of the substance and its metabolites to accumulate in the tissues of exposed organisms is of particular concern, with potential effects on ecosystems and human health. This review aims to provide an updated summary of the available knowledge on the ecotoxicological effects of cocaine in aquatic ecosystems, highlighting existing knowledge gaps and the need for further research.

Keywords: cocaine; emerging contaminants; aquatic pollution; physiological damage; oxidative stress

1. Introduction

Over the past two decades, emerging contaminants have been detected in various environmental compartments around the world, including surface and ground waters, sediments, soils, and the atmosphere as well as in a wide range of consumer products [1–3]. Emerging contaminants are naturally occurring or synthetic chemicals which, although they have been present in the environment for an extended period, have only recently been identified and characterised. Their presence in aquatic ecosystems poses a threat not only to aquatic life, but also to humans and the environment [4]. This issue has become of interest to the society, public health authorities, industry, and the agricultural sector, due to the potential risks associated with long-term and low-dose exposure [5].

The occurrence of emerging contaminants in natural ecosystems has only been investigated in the last 20 years due to the lack of sensitive analytical methods able to detect their relatively low levels (typically in the range

of ng/L and ug/L). However, these pollutants are widely distributed in aquatic and terrestrial environments but are not commonly monitored in the environment [6]. Recent studies demonstrated that, even at low concentrations, these contaminants are able to cause adverse effects on both ecological and human health [7,8]. Emerging contaminants include anthropogenic and naturally occurring chemicals [9,10], pharmaceuticals [11,12] and personal care products (PPCPs) [13], metabolites and transformation product of PPCPs [14], illicit drugs [15–17], engineered nanomaterials [18], and antibiotic resistance genes [19].

Among these, illicit drugs [20] have been defined by The United Nations Office on Drugs and Crime as substances whose possession, manufacture, sale or consumption is prohibited by law, considering the way these substances are produced, distributed and acquired and their use for non-medical purposes [8]. Illicit drugs and their metabolites are substances characterised by different chemical structures, capable of causing an extremely high potential biological effect on non-target organisms and humans [21]. Based on their effects, illicit drugs can be classified as hallucinogens (e.g., 3,4-methylenedioxyamphetamine or MDA, 3,4-methylenedioxymethamphetamine or MDMA, lysergic acid diethylamide or LSD), stimulants (e.g., cocaine or COC, benzoylecgonine or BE, norcocaine or NCOC, norbenzoylecgonine), opioids (e.g., morphine derivates, heroin, 6-acetyl-morphine, codeine, norcodeine, oxycodon), and other psychoactive drugs as cannabinoids (THC-COO, THC) [7].

These substances have been detected in influents and effluents waters of wastewater treatment plants (WWTPs), drinking water [22], and both freshwater and seawater [23,24]. Illicit drugs include synthetic pharmaceutical compounds and plant-derived substances, and their use for non-medical purposes is prohibited by national or international laws considering the risk they can cause to users [25,26]. The increasing production and use of these chemicals is leading to severe environmental impacts due to the continuous release of parent compounds, metabolites, and precursor compounds [26].

The occurrence of illicit drugs and their metabolites in aquatic ecosystems may be related to human social behaviour and tourism patterns. Several studies [27–29] have shown that during holidays, weekends, and mass events such as music festivals, the use of illicit drugs increases significantly, highlighting how consumption is higher during recreational periods [30].

Illicit drugs share several characteristics with pharmaceuticals. Indeed, these compounds exhibit similar sources of contamination, polar chemical structure, environmental persistence, and biological activity. It has been estimated that approximately 200 million individuals worldwide use illicit drugs, with consumption levels comparable to those of therapeutic pharmaceuticals. Consequently, these substances can be detected in the environmental matrices at concentrations like pharmaceuticals [31].

In the study by Zhao et al. [32], environmental concentrations of illicit drugs and their metabolites were quantified in urban wastewater in Xinjiang, China. Methamphetamine concentrations ranged from 2.60 to 10.02 ng/L, while MDMA, COC, and BE were found within ranges of 0.49–6.87 ng/L, 0.48 ng/L, and 1.12–2.45 ng/L, respectively. Additionally, Melones-Peña et al. [33], detected these compounds in WWTPs effluents in Madrid, reporting concentrations of 0.06 and 0.10 μg/L for methamphetamine, 0.07, 0.11 and 0.15 μg/L for MDMA, 0.01, 0.02 and 0.06 μg/L for COC, and 0.01 and 0.02 μg/L for BE, respectively. In coastal waters of Santa Catarina, Brazil, COC and BE were detected at concentrations of 0.02–0.17 ng/L and 0.01–1.1 ng/L, respectively, as reported by Pisetta et al. [34].

According to Jones-Lepp et al. [35], methamphetamine and MDMA have been detected in the effluent from WWTP with a concentration of 2 and 0.5 ng/L, respectively. Whereas, according to Zuccato et al. [36], levels of COC and its metabolite (BE) were detected in surface waters at 120 ng/L and 750 ng/L, respectively.

Since the publication of these earlier reports, there has been considerable increased interest in measuring drug levels in the environment as the presence of illicit drugs has been detected throughout the world.

According to data provided by the United Office on Drugs and Crime (UNODC), the most widely used drug worldwide is cannabis, followed by COC, amphetamine-group substances, and opiates. In addition, abundant residues of benzoylecgonine, ecgonine methyl ester, MDMA, methamphetamine, amphetamine, and morphine have been found in the effluents of WWTPs [37].

Similarly to pharmaceuticals, human consumption is the main source of contamination for illicit drugs, while uncontrolled discharges related to the manufacture of these substances are minor sources [36]. Following consumption, illicit drugs are partially metabolized and excreted in urine and faeces as unchanged parent compounds or active metabolites, which first enter sewage systems and subsequently reach the WWTPs [24].

In developed countries and only in a small proportion of developing countries WWTPs serve as a primary gateway for illicit drugs and their metabolites entering the aquatic environment [9]. In fact, in most developing countries, due to a lack of financial resources and updated technology, water bodies are the main source of waste accumulation, as there are effectively no WTTS in place [25]. Because many facilities are not designed to eliminate these specific contaminants, they are continuously released into natural water bodies, posing a threat to ecosystem

health [38]. The environmental fate of these drugs is largely influenced by their chemical properties; their polarity and moderate lipophilicity allow them to remain in the water column or adsorb onto organic matter such as sludge and sediment. Notably, their presence is not limited to water; they have also been detected in airborne particles globally, notwithstanding their limited volatility [31].

Contaminant degradation and removal efficiency depend on both WWTP operational conditions (e.g., hydraulic retention time and kinetics) and environmental variables such as pH and temperature [39]. Additionally, the partitioning behavior of these compounds is governed by their physical-chemical properties [40]. Compounds with a log K_{OW} < 3.0 generally persist in the aqueous phase, while those with higher lipophilicity tend to bind to sludge and organic matter [41].

Furthermore, illicit drugs can interact with residues of other therapeutic substances, causing unexpected pharmacological interactions that could have synergistic toxic effects on aquatic organisms [42]. The presence of illicit drugs in the aquatic ecosystems is a matter of considerable importance for the scientific community, given their potential impact on the environment [8].

Although numerous studies have reported the occurrence of COC and its metabolites in aquatic ecosystems, the available data remain highly fragmented and difficult to compare. Reported concentrations vary by several orders of magnitude. Moreover, most studies are limited to surface waters, while sediment, biota, and trophic-transfer assessments are still scarce. These inconsistencies highlight the need for a critical analysis to clarify methodological limitations and determine which environmental compartments and species are at highest ecological risk. Therefore, this review aims not only to critically evaluate the ecotoxicological effects of COC and its metabolites on aquatic organisms and ecosystems, but also highlights the importance of analytical innovation as a cornerstone for determining the actual ecological risk and developing more effective monitoring strategies in order to address current knowledge gaps.

2. Materials and Methods

This review was conducted through careful bibliographic research on major scientific search engines, such as PubMed and Google Scholar, taking into account articles published between 2010 and 2025, always giving priority to the most recent articles. The words used to obtain the best results were: “emerging contaminants”, “cocaine”, “water pollution”, “illicit drugs”, “effects”, “aquatic organisms”, “reproduction”, “health” and various combinations of these.

3. Cocaine

Cocaine is a powerful psychostimulant of natural origin, belonging to the class of alkaloids. Its psychoactive substance is extracted from the leaves of coca (*Erythroxylon coca*), a plant native to South America. The traditional use of coca by indigenous peoples dates back over 5000 years. It is mainly consumed by chewing fresh leaves or preparing teas and infusions, practices that allow the release of the alkaloid responsible for the stimulating effect [43].

In addition to its stimulating effects, indigenous populations attribute healing and regenerative properties to coca. In fact, nowadays, these populations still use this substance to alleviate the symptoms of high-altitude sickness [44].

COC was isolated in the 19th century for the first time. Immediately, it arouses the interest of the medical community, which initially used it for its anaesthetic properties and then as a remedy for various conditions, such as toothache, headache, and gastrointestinal disorders [45].

During this period, the use of COC became part of everyday life for the general population, aided by the ease of purchase and, above all, the wide range of uses for which it was popular [46].

The widespread use of COC brought to light the dark side of this substance, i.e., the addiction along with many side effects, such as cardiac damage, neurological and mental damage, examples of which are shown in Table 1 [47–49].

Table 1. Short-term and long-term effects in humans.

Short-Term Effects	Long-Term Effects
Increased heart rate	Cardiovascular damage
Euphoria and hyperactivity	Neurological deterioration
Agitation and paranoia	Mental disorders
nosebleeds	Depression
Loss of smell	Respiratory problems
Anxiety and hallucinations	Malnutrition
	Gastrointestinal problems

Recreational use and the increase in cases of abuse prompted the scientific community to reevaluate cocaine's image as a "miracle drug" and recognize how dangerous it really was. As a result, every formulation containing COC was removed from the market [50].

The stimulant effect of COC, as reported by Heard et al. [51], stems from its binding to monoamine transporters, thereby blocking the reuptake of dopamine, noradrenaline, and serotonin in the presynaptic nerve cell. This increases their concentration in the synaptic cleft, leading to hyperstimulation of postsynaptic receptors and feelings of euphoria. Its reinforcing properties and addictive potential are primarily linked to increased dopamine levels. However, this effect is temporary, as homeostatic mechanisms, including the activation of dopaminergic autoreceptors, reduce its synthesis and release, promoting tolerance and seeking behaviour. The toxic effects arise from interactions with various molecular targets, including acetylcholine muscarinic receptors, voltage-gated ion channels, and the GABA and glutamate systems, contributing to neurotoxicity, cardiotoxicity, and alterations in neuronal activity [52].

On the other hand, the toxic effects of the substance derive mainly from its interaction with various molecular targets, such as muscarinic acetylcholine receptors, which act as agonists and generate neurotoxicity. In addition, COC interacts with voltage-dependent ion channels, a mechanism underlying its anaesthetic properties and cardiotoxic effects. Finally, recent studies suggest the involvement of the GABA and glutamate systems, the main inhibitory and excitatory neurotransmitters in the brain, explaining the deterioration of general neuronal activity [51].

Currently, the use of COC in medicine is severely restricted. There is only one product containing COC hydrochloride on the market, a nasal anaesthetic solution used to reduce mucosal bleeding during specific surgical and diagnostic procedures. Approved in 2017 by the Food and Drug Administration (FDA), CDER (2017 Drug and Biologic Calendar Year Approvals), it is the only cocaine-containing drug currently authorized. However, its use is rare given the availability of safer and more effective alternatives [43].

Despite its limitations in the medical field, COC is among the most widely used psychoactive substances globally. In 2024, COC became part of the lives of approximately 19 million people aged between 15 and 64 (UNODC, 2025), who find it available on the shelves of the illegal market [53].

COC is sold illegally and is available in two forms i.e., white powder, chemically known as cocaine hydrochloride (whose chemical structure is shown in Figure 1), which is mainly consumed intranasally, and in solid form, which consists of its free base, known as "crack," generally smoked [54].

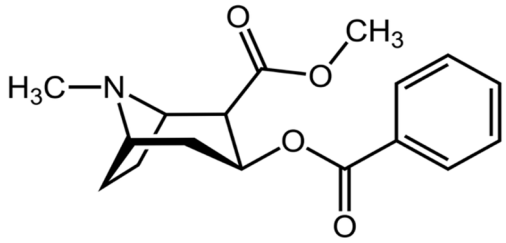

Figure 1. Chemical structure of cocaine hydrochloride.

Cocaine Presence in Aquatic Ecosystem

The growing consumption of COC has led to its inevitable presence in aquatic environments. After ingestion, COC is rapidly metabolized, producing various metabolites such as benzoylecgonine (BE, 45% of the dose), and ecgonine methyl ester (EME, 40%) [55].

Following hepatic metabolism and excretion, COC and its metabolites enter the sewage system via urine and faeces. If not adequately treated, they end up in the sea or in freshwater courses [37].

Several studies [22,56–58] have investigated COC concentrations in surface waters, with concentrations ranging from approximately 0.13 ng L^{-1} to 6.7 ng L^{-1} recorded in freshwater [59–61], in coastal areas, however, concentrations ranging from 2.4 ng L^{-1} to 537 ng L^{-1} were recorded [26,62–64].

These data highlight how the presence of COC is a widespread phenomenon globally, with concentrations varying considerably [63].

The presence of COC in aquatic environments is often associated with the discharge of inadequately treated wastewater, but it can also originate from clandestine refineries [8,65], and from voluntary or involuntary spills, the latter of which can become localized sources of toxicity that marine fish and reptiles such as sharks and turtles can potentially encounter [66].

Once in the environment, COC can undergo biological and photochemical degradation processes, but its persistence even at low concentrations can pose an ecotoxicological risk to aquatic fauna, altering the behaviour

and physiology of organisms [67,68]. In aqueous conditions, COC degrades relatively rapidly, with a half-life ranging from a few hours to around one day, whilst its main metabolite, benzoylecgonine, is significantly more persistent, with retention times ranging from several days to weeks, depending on environmental conditions, thereby increasing the likelihood of chronic exposure for aquatic organisms [69].

The wide variability in reported concentrations (0.13 ng/L to 537 ng/L) suggests that environmental distribution is strongly influenced both, by consumption trends and also by the efficiency of wastewater treatment plants and the physicochemical characteristics of aquatic systems. However, many studies rely on single-time sampling campaigns, making it difficult to establish temporal trends or quantify chronic environmental loading. Additionally, the lack of harmonized analytical protocols limits cross-study comparability and may lead to underestimation of persistent metabolites. In fact, whilst monitoring COC and its metabolites in surface waters is simpler and is carried out frequently, this proves far more complex in sediments and organisms (e.g., in adipose tissue). However, advances in analytical chemistry have enabled the development of new, highly sensitive and specific techniques, such as liquid chromatography coupled with mass spectrometry (LC-MS), which allows the detection and quantification of analytes in very small traces and enables the distinction between the parent compound and its metabolites within environmental samples. The application of these techniques makes it possible to overcome the limitations associated with complex matrices, providing a more realistic picture of environmental contamination. Furthermore, this could lead to a better understanding of which species are most vulnerable to ecological risk posed by the presence of COC and its metabolites in the environment.

4. Cocaine Effects on the Physiology of Aquatic Organisms

The continuous presence of COC in aquatic environments can cause physiological stress caused by biochemical imbalances [70] all of which compromises the growth, reproduction, and overall health of exposed organisms [71], contributing to serious biodiversity loss [72]. The toxicity of COC affects both simpler organisms such as microcrustaceans and mollusks [67,71], but also more complex organisms like fish [73].

In addition to direct effects on organisms, as in the case of sea urchins (*Echinometra lucunter*) reported by da Silva Souza et al. [74], there is evidence of damage to reproduction, with possible serious repercussions on food chains, as COC undergoes a process of biomagnification that can compromise public health [75].

4.1. Effects on Neuroendocrine Systems

Despite the low environmental levels of COC and its metabolites in freshwaters, they still pose a threat to aquatic life. Their occurrence in surface waters, often as part of a complex mixture with other therapeutics, can trigger unpredictable interactions and various toxic effects in non-target species [76].

Specifically, two distinct metabolic pathways are involved in the biotransformation of COC in humans. The first involves the hydrolysis of ester groups, while the second is an oxidative pathway targeting the amine group, which is implicated in specific toxic responses [77]. In addition to COC itself, several metabolites participate in these processes, including norcocaine, norcocaine nitroxide, N-hydroxynorcocaine, norcocaine nitrosonium, cocaine iminium, and formaldehyde [78]. In both cerebral and hepatic tissues, microsomal enzymes, including the cytochrome P450 complex, catalyse reactions involving specific metabolites, like norcocaine nitroxide and N-hydroxy derivative, which trigger the subsequent generation of superoxide and lipid peroxyl radicals [79,80]. Furthermore, the ultimate consequence of these processes is lipid peroxidation (LPO), which results in the production of malondialdehyde (MDA) [81]. This toxic byproduct further contributes to the generation of reactive oxygen species (ROS), leading to significant structural damage to cellular membranes [82]. The use of biomarkers for each level of cellular organization allows for the evaluation of the first signs of biological effects in environmental assessment [70].

4.1.1. Mussels

Mussels are organisms susceptible to contamination due to their filter-feeding behaviour [83–88].

The study conducted by Fontes et al. [89] found a decrease in AChE activity in mussels exposed to COC at concentrations of 0.2 μg L^{-1} and 2.0 μg L^{-1}. This decrease is a typical reaction that occurs in mussels following exposure to environmental contaminants [90]. Acetylcholinesterase (AChE) is involved in the hydrolysis of the neurotransmitter acetylcholine into choline and acetate and plays an important role in the cholinergic system [91]. In these organisms, AChE is one of the most effective biomarkers involved in the assessment of neurological changes caused by xenobiotics [92]. Following the decrease in AChE activity, a state of relaxation is also observed in mussels [93]. In fact, in the study conducted by Fontes et al. [89] mussels exposed to COC close their valves with less rigidity. This pattern could indicate a difficulty in metabolising COC which, due to its hydrophobic

nature, become bioaccumulate in the biota [94]. Furthermore, COC appears to interfere with dopamine (DOPA) and serotonin (5-HT) levels, causing their increase in exposed mussels [95]. The dopaminergic and serotonergic systems are involved in a series of processes such as the regulation of stress response in both invertebrates and vertebrates [95]. In mussels, indolamine serotonin (5-HT) and the catecholamine dopamine (DOPA) neurotransmitters regulate physiological processes such as, sexual differentiation, spawning, gamete development, reproduction, relaxation, and opening the mussel siphon and adductor muscle [96]. Furthermore, DOPA and 5-HT appear to have some influence on the beating of the ciliary of mollusk larvae, affecting their ability to absorb food [97].

De Felice & Parolini [98] investigated the oxidative status in the gills and digestive gland of *Mytilus galloprovincialis* following exposure to COC and its major metabolite, benzoylecgonine (BE), at environmentally relevant concentrations. The study reported a slight modulation of the oxidative status in both the gills and digestive gland. This differential organ response is biologically pertinent, given the established roles of these tissues in pollutant interaction. In fact, the gills are the first organ of contact for environmental contaminants [99], while the digestive gland is directly involved in the pathways of phases I and II of xenobiotic metabolism [100]. Because of this, the gills respond more acutely to illicit drugs; for instance, antioxidant enzyme activity is modulated within 48 h of COC and BE exposure. However, in the digestive gland these biochemical changes only manifest after extended exposure periods [101].

The most pronounced enzymatic changes were observed in the gills. Specifically, exposure to the mixture resulted in a very high increase in SOD activity. This is explained by the high production of superoxide anion caused by exposure to MIX rather than to individual molecules [92]. Following the activation of SOD in gills, hydrogen peroxide may be produced, which is subsequently degraded by CAT and GPx [102]. For this reason, it is believed that this may have led to an increase in GPx activity after 48 h of exposure to the mixture [98]. Furthermore, after 96 h of exposure to both BE and MIX, a significant inhibition of GPx was observed in gills compared to the control [92]. As reported in previous studies, this could be related to the duration of exposure and/or the concentration used. In fact, short-term exposure or low concentrations could lead to an increase in enzyme activity, whereas long-term exposure or high concentrations could inhibit it [103]. On the other hand, no significant changes were found in CAT activity. This could be because at the end of exposure to both MIX and BE, H_2O_2 levels were too high to be compensated by GPx, but at the same time were not high enough to induce CAT activation. Although CAT and GPx play a complementary role in the degradation of hydrogen peroxide, their response may differ due to the competition for the same substrate and/or to the difference in the affinity for the H_2O_2 [104].

4.1.2. Crustaceans

Recent ecotoxicological studies have highlighted the adverse effects of COC on freshwater invertebrates, critical components of aquatic food webs. De Felice et al. [71] demonstrated that exposure to environmentally relevant concentrations of COC (50 ng L^{-1} and 500 ng L^{-1}) not only caused oxidative imbalance but also negatively impacted the swimming activity of the cladoceran *Daphnia magna*.

Exposure to COC at both concentrations triggered pro-oxidative stress by stimulating ROS production and altering the activity of the primary antioxidant enzymes: SOD, CAT, and GPx [102]. The significant decrease in SOD activity observed at the higher concentration suggests a buildup of superoxide anions (O_2) caused by an initial surge in ROS [99,105,106]. This decrease might also be explained by negative feedback or direct inhibition caused by the accumulation of hydrogen peroxide (H_2O_2) [107]. Notably, H_2O_2 levels can increase not only through enzymatic action but also via spontaneous dismutation and peroxisonal enzymatic pathways [108,109]. The increase observed in GPx activity also supports the hypothesis of H_2O_2 production. On the contrary, no activation of CAT was detected. Both GPx and CAT are involved in metabolizing hydrogen peroxide, but their response may differ due to competition for the same substrate [110]. They may also exhibit different activity in relation to the levels of H_2O_2 to be counteracted. In fact, while GPx acts even when H_2O_2 levels are low, CAT can only be activated at high concentrations of this pro-oxidant molecule [96]. Furthermore, an increase in GST activity was observed, suggesting the involvement of phase II enzymes in COC detoxification processes [71]. Exposure to COC also induced significant adverse effects at the individual level [110], particularly affecting the locomotor and swimming activity of *Daphnia magna*. The response was distinctly concentration-dependent, as lower concentration had a stimulatory effect, resulting in an increase in distance moved and swimming speed, whereas higher concentration had a negative and toxic effect, reducing both endpoints [71]. This bimodal dose-response pattern is consistent with the property of COC as a psychomotor stimulant drug [52].

Given the pivotal role of *Daphnia magna* in freshwater ecosystems as a primary consumer, the observed neurotoxicological and behavioural impairments caused by environmental COC exposure are critical. Such

adverse effects may propagate through the trophic chain, potentially impacting higher-level organisms and destabilizing ecosystem dynamics [71].

The effects of COC and its metabolite BE had been investigated in the crayfish, *Procambarus clarkii*, a species generally regarded as highly tolerant to external stressors [111]. De Felice et al. [112] examined the response of the crayfish to two environmentally relevant concentrations (50 ng/L and 500 ng/L). The findings highlight key interspecific differences in sensitivity compared to the more responsive *D. magna*.

Unlike the significant oxidative stress reported in *D. magna*, no significant change in lipid peroxidation levels was observed in the gills or digestive glands of the exposed crayfish. This suggests the antioxidant defences in *P. clarkii* successfully prevented damage to cellular macromolecules. The protective mechanisms appear to involve a significant activation of the antioxidant enzyme SOD. Specifically, exposure to higher concentration of BE resulted in a significant induction of SOD activity in the gills [112]. This indicates that the metabolite BE may have induced the overproduction of superoxide anion, whose toxicity was effectively counteracted by SOD. Furthermore, the limited production of hydrogen peroxide as a byproduct of the SOD reaction [110] explains the lack of activation of subsequent detoxification enzymes, CAT and GPx.

However, considering that several licit and illicit drugs can induce neurotoxic effects, such as reduced neurotransmitter production [113], COC could exert its toxicity in this regard due to its psychostimulant activity. Previous studies conducted on invertebrates [114] and vertebrates [115] have established that exposure to COC and BE induces significant inhibition of AChE activity [112]. AChE plays an extremely important role in various biological functions, including growth, motility and feeding activity, so inhibition of this neurotransmitter could have negative consequences on individual behaviour [114].

The study conducted by De Felice et al. [112], indicates that COC exposure improves crayfish responsiveness to visual stimuli. The effects were concentration dependent, in fact low concentrations reduced rapid cheliped attacks, while high concentrations increased them. This increase is likely attributed to the drug's excitatory impact, raises the animals' state of alert and boldness [116]. It may also be possible that these results are related to the loss of nerve conduction ability caused by AChE inhibition, which could have induced a state of hyperactivity [117].

Most notably, COC exposure resulted in a significant decrease in the frequency with which individuals consumed administered food [105]. The altered behavior could be attributed to increased levels of the neuropeptide CART, an appetite-modulating peptide with effects mimicking those of psychostimulants [118]. In treated crayfish, COC exposure likely promoted CART production, leading to suppressed feeding through a perceived sense of fullness. Furthermore, the drug's direct impact on the nervous system-specifically the modulation of dopamine and serotonin signaling-may play a primary role in this behavioral inhibition. In fact, by blocking the normal recycling processes of serotonin, dopamine and norepinephrine, COC can induce the inhibition of the re-uptake [119]. Crayfish exposed to COC may show increased dopamine levels, which could lead to inhibition of feeding behaviour. These results highlight how exposure to COC significantly altered the feeding behaviour of crayfish.

The contrasting responses observed at 50 ng/L and 500 ng/L highlight a clear dose-dependent and bimodal toxicological profile, consistent with the psychostimulant activity of COC. Importantly, the lower concentrations tested fall within environmentally realistic levels reported for freshwater ecosystems, indicating that behavioural alterations in zooplankton may be ecologically relevant. Conversely, the limited oxidative damage observed in crayfish suggests species-specific resilience, pointing to the need for comparative sensitivity analyses across different trophic groups.

4.1.3. Fish

Exposure to environmental concentrations (0.04, 0.4, 4 and 40 nM) of COC and its principal metabolites, BE and ecgonine methyl ester (EME), has been shown to induce significant primary genetic damage in zebrafish embryo cells [76]. The study demonstrated a notable increase in DNA fragmentation following exposure, confirming the ability of the compounds to exert genotoxic effects that may become fixed genetic damage [120]. This cytogenotoxicity was corroborated by a significant increase in the frequency of apoptotic cells, suggesting that the induced damage exceeded the cellular repair capacity and triggered programmed cell death. The cyto-genotoxic effects could be related to an overproduction of ROS [76], probably because of the biotransformation of COC in norcocaine nitroxide and N-hydroxy norcocaine by cytochrome P450 activity [121]. Furthermore, COC metabolites may be involved in the activation of redox cycles, the depletion and/or decrease of antioxidant enzymes, and the consequent overproduction of ROS, resulting in oxidative damage, disruption of cellular activity and organ damage [122], as supported by the data obtained.

Chronic exposure of European eels to environmentally relevant concentrations (20 ng L^{-1}) of COC induce systemic toxicity, targeting crucial organs such as skeletal muscle, kidney, and liver [68,123].

Consistent with its known properties as a psychomotor stimulant in humans [52], COC exposure in eels increased motor activity, increasing vigilance and alertness, often manifesting as accelerated swimming. However, chronic exposure leads to severe histological damage in both red and white muscle fibres, which show signs of injury [68]. These alterations appear to be like those caused by a syndrome known as rhabdomyolysis, characterized by breakdown of the muscle fibres and dispersion of intracellular components, including the enzymes CK, LDH, and AST, myoglobin and electrolytes, into the circulatory system [124]. This diagnosis was strongly supported by the analysis of serum levels of CK, LDH and AST, which had indeed increased [68]. Cocaine-induced rhabdomyolysis could occur either through a direct effect of the drug on the muscle and/or through repeated ischemic events mediated by the vasoconstrictor properties of COC and its metabolites [68].

Reperfusion following ischemia inflicts secondary damage by producing free radicals that bypass the muscle's natural antioxidant defences [68]. As the sarcolemma and muscle fibber membranes degrade, cytosolic enzymes are released into the body [125]. A critical consequence of this membrane disruption is the massive leakage of myoglobin into the bloodstream [126]. Once myoglobin levels surpass the plasma's binding threshold, the protein precipitates within the kidneys, causing tubular obstruction and acute renal failure [127]. This pathological pathway reinforces the link between chronic COC exposure and renal impairment in *A. anguilla* [68].

The available data show that zebrafish embryos exhibit genotoxic and oxidative effects at concentrations ranging from 0.01 to 10 μg/L, while European eels display muscular, hepatic and renal alterations at environmentally relevant levels (20 ng/L). These findings indicate that early-life stages are substantially more sensitive, but also that adult fish can be affected at concentrations actually detected in surface waters. Subsequent studies confirmed that chronic COC exposure also induces damage in the liver and kidney [123], crucial organs for xenobiotic metabolism and excretion [128]. Cocaine-induced hepatotoxicity is correlated with the production of NCOC and N-hydroxynorcocaine, and with the direct oxidative damage caused by ROS that are produced during the redox cycles of the metabolic cascade [129]. In some cases, cocaine-induced nephrotoxicity has been reported to be correlated with rhabdomyolysis, hyperthermia or ischemia caused by vasoconstriction [129]. Therefore, it is possible that the changes observed in the kidney of eels following cocaine-exposure are in part correlated to muscle injury [123]. Alternatively, COC could exert direct cytotoxic effects on the kidney in the form of the metabolite EME or, to a lesser extent, in the form of NCOC [129].

A key finding in the liver was the analysis of GRP78, the primary marker of endoplasmic reticulum (ER)-stress [130]. GRP78 acts also as an apoptotic regulator by protecting the host cell against ER stress-induced cell death. A slight increase in GRP78 expression was observed during exposure, followed by a marked increase in the post-exposure recovery phase [123]. This increased GRP78 expression correlated inversely with the decreasing caspase-3 levels during recovery, suggesting that the expression of GRP78 acts to inhibit caspase-3 activity. Upon the interruption of cocaine-exposure, liver cells promote the expression of GRP78, which can restore the condition of homeostasis and counteract apoptosis and the consequent tissue damage [123].

Furthermore, blood glucose levels were also analyzed, as glucose represents a marker of stress response [123]. Indeed, a consistent increase in blood glucose levels was found in both cocaine-exposed and post-exposure recovery eels, likely a general stress response of the fish to pollutant effects [131]. COC increases plasma glucose levels through the release of catecholamines [132,133], and supporting this, a consistent increase in plasma catecholamines was found in the eels.

4.2. Immune System

Exposure to COC in aquatic organisms causes an anaesthetic effect, which leads to an alteration of the neuroendocrine and cardiovascular systems, with a consequent impact on the immune response, whether adaptive or innate [134].

Similar to what happens in mammals, COC modulates the immune response through dysregulation of the hypothalamic-pituitary-adrenal axis and modulation of the monoamine system [114].

Monoamines such as serotonin modulate the production of key immune system cells such as cytokines, phagocytes, granulocytes, and macrophages, indicating a consequent alteration of immune system-related processes [135]. Added to this is the downregulation, observed in *Danio rerio* exposed to COC, of several proteins of the major histocompatibility complex class I, as well as immune mediators such as interleukin-1 beta [136]. Moreover, in *Danio rerio*, a downregulation of genes involved in the immune response and inflammatory processes has been highlighted, including *ccl20b*, *ccl20a.3*, and *nos2a*. RNA-seq analysis conducted on larvae exposed to COC revealed differential expression of numerous genes and alterations in multiple pathways, including those related to innate immunity, immunosuppression and neuroinflammation [137].

Furthermore, evidence come from the study by Capaldo et al. [123], an increase in blood ALT and PCR values was recorded in eels exposed to COC. ALT is a marker of liver function [124], so its increase is an indication of liver damage, with all that this entails. CRP, on the other hand, is a protein involved in innate immunity [125], and is therefore considered a bioindicator of the general health of fish. The increase in this protein in eels confirmed an alteration in the immune response following exposure to the drug [126].

Exposure to COC also modulates the expression of genes and proteins involved in the inflammatory response, such as the CCL2/CCR2 pathway, thus altering macrophage recruitment [138]. Taken together, these findings suggest that COC is a potential source of immunotoxic stress for aquatic organisms, thereby compromising their survival.

4.3. Effects on Reproduction and Embryonic Development

The presence of COC in aquatic environments may pose a potential risk to the reproduction of various aquatic species. Recent studies have highlighted how the substance can interfere with reproductive processes.

4.3.1. Fish

For instance, Fontes et al. [139] have documented histological alterations in the gonads of eels (*Anguilla anguilla*) following exposure to COC (20 ng L^{-1}). Eels showed reduced follicular maturation and changes in the expression and localization of key enzymes involved in oogenesis and steroidogenesis (aromatase P450, 17β-HSD, 3β-HSD), accompanied by changes in serum levels of gonadotropins and cortisol. This suggests a direct impairment of ovarian activity and a potential inhibitory effect mediated by the dopaminergic system, capable of interfering with endocrine regulation of reproduction.

4.3.2. Mussels

The alteration of the neurotransmitter's dopamine and serotonin, following exposure to COC, led to a reduction in gonadal maturation even in mussels Perna perna [140].

4.3.3. Crustaceans

Negative effects on reproduction have also been observed in simpler organisms such as the invertebrate *D. magna*. Indeed, De Felice et al. [71] reported reduced reproductive success in daphnia exposed to COC (50 ng L^{-1}), hypothesizing a shift in energy balance toward highly modified swimming activity, or a direct toxic effect on reproductive organs. They have shown that exposure to the main metabolite of COC, benzoylecgonine, induces oxidative stress, inhibition of acetylcholinesterase activity, and behavioural changes that result in reduced fertility.

Overall, these studies indicate that COC and its derivatives can compromise reproduction in both invertebrate and vertebrate aquatic organisms through multiple mechanisms, including endocrine dysfunction, oxidative stress, and behavioural changes, with potential repercussions on population dynamics and the stability of ecosystems.

4.3.4. Embryonic Development

Similar to studies on rats [141], in which altered embryonic development was documented, the effect of COC on fish embryos, particularly zebrafish (*Danio rerio*) embryos, was investigated [76,142,143].

The study conducted by Parolini et al. [76] highlighted alterations in *D. rerio* exposed to COC (ranging from 0.01 μg/L to 10 μg/L) related to morphological and functional defects, including abnormalities in the development of the central nervous system, cardiovascular malformations, and delays in embryonic growth. In addition, changes were observed in the gene expression of numerous markers involved in the genesis of the nervous and cardiovascular systems, suggesting that early exposure to COC may interfere with key embryonic development processes.

4.4. Bioaccumulation and Biomagnification

Illicit drugs, along with their metabolites, are continuously released into the aquatic environment, after consumption and excretion [132], via wastewater treatment systems, which do not always present optimal efficiency [38,133]. Furthermore, the presence of COC packages on the shores, which are not recovered by vendors or authorities [66], also constitutes a source of entry into the aquatic environment.

Once released into aquatic ecosystems, these substances can be absorbed (or taken) by aquatic organisms, within which they subsequently are accumulated. Several studies reported phenomena of bioaccumulation of chemical compounds in aquatic organisms considered important nutritional resources for humans, such as bivalves, crustaceans, cephalopods, and fish [134,135]. Through the trophic chain, these substances can reach humans, who may therefore be chronically susceptible to exposure [144].

Due to multiple interacting factors, it is challenging to determine the specific causes that govern the bioaccumulation of Pharmaceutical Active Compounds (PhACs) in aquatic organisms. Furthermore, bioaccumulation also depends on the compound's concentration in the water, the environmental pH, the bioconcentration factor (BCF), the bioaccumulation factor (BAF), and the compound's log K_{OW} [145]. The bioconcentration factor (BCF) refers to the process by which a water-borne chemical is accumulated by an aquatic organism [145]. The bioaccumulation factor (BAF) is an important tool which refers to the concentration of a chemical substance in an organism with its corresponding concentration in the surrounding environment (e.g., water, sediment, or food) under equilibrium conditions [146]. Based on their physico-chemical properties, contaminants are capable of being accumulated in organisms. One of the most frequently used parameters to estimate a contaminant's potential bioaccumulation is the log K_{OW} (octanol-water partition coefficient), in relation to which a higher value correlates with a greater bioaccumulation capacity of the contaminant [147]. According to the results reported by Fontes et al. [89], the log K_{OW} for COC shows an increase from 0.10 (ionic form) to 2.30 (non-ionic form). This is because, given the alkaline pH of marine waters and pKa of COC (pKa= 8.61), the compound tends to be partially present in its non- ionized form, due to the pH value observed in the sampling area [24]. Therefore, by virtue of the alkaline pH of the marine waters and pKa of COC, the compound displays a greater propensity for bioaccumulation owing to its moderate hydrophobicity [148].

Mussels are filter-feeding organisms, a mechanism through which they can accumulate pathogenic bacteria, as well as organic and inorganic particles dissolved in the water column or adhered to the sediments [149]. Due to these characteristics, they are widely employed as sentinel organisms for environmental monitoring [150]. Several studies have documented the presence of metals, PAHs, microplastics [146], pharmaceuticals, illicit drugs such as COC and BE in superficial water [22,58], which suggests that the seafood organisms may be susceptible to contamination. Similarly to several previous investigations [151,152], the results reported by Fontes et al. [89] revealed that COC was detected in all mussels' samples, with concentrations ranging between 0.914 μg Kg^{-1} and 4.58 μg Kg^{-1} (ww).

According to the findings reported by Roveri et al. [153], the highest drug concentrations were detected in demersal species rather than in pelagic species, considering that greater concentrations tend to be deposited in the deeper layers of the water [153]. In addition, body size also plays an important role, as a smaller size reflects a lower trophic level and, consequently, a lower degree of biomagnification compared to others [154].

Capaldo et al. [155] assessed the ability of European eel to bioaccumulate COC into the tissues after exposure to environmental concentrations of this substance, which was reported to be highly abundant in surface water. Indeed, after one month of exposure, COC was found in the eel's tissues. Higher concentrations of COC were detected in the brain (30.50 ± 0.36 pg/g), muscle (20.17 ± 0.47 pg/g), liver (13.4 ± 2.17 pg/g), and kidney (11.43 ± 1.18 pg/g), while lower concentrations were found in the digestive tract (8.87 ± 0.74 pg/g), gills (5.57 ± 0.74 pg/g), skin (4.87 ± 0.18 pg/g), spleen (0.61 ± 0.3 pg/g), and gonads (0.47 ± 0.15 pg/g). According to the results obtained, COC can accumulate within the eel's tissues only at very low concentrations, suggesting a risk to its health. Furthermore, the cells would likely return to a physiological state only after a long recovery period following the interruption of exposure, given that COC was still present in the eel's tissues after three days of recovery following the interruption of exposure.

Muscle and liver of eels showed high levels of COC after exposure, and this could be correlated with the fat content present in these tissues. In fact, although COC is generally highly hydrophilic, drug-related victims show COC accumulation in adipose tissue and skin [156]. Its bioaccumulation could influence eels' physiology and considering that COC effects are mediated by dopaminergic receptors [157], COC may interfere with reproductive processes in which dopamine plays a key role [157].

Compared to the existing literature data regarding the phenomenon of bioaccumulation in bony fish [141], reports are practically absent for cartilaginous fish, such as sharks and rays. Sharks and rays are important constituents of marine ecosystems, where they play the role of predators in the trophic web and are considered sentinel species for environmental contamination [158]. Furthermore, they represent a nutritional protein source and are therefore consumed extensively worldwide [159]. However, due to commercial fishing activities, these species are increasingly threatened and may face extinction [160]. de Farias Araujo et al. [73] conducted an exploratory analysis concerning the presence of COC and its main metabolite BE in the muscle and liver tissue of a small coastal shark species, considered vulnerable by the International Union for Conservation of Nature (IUCN), namely Brazilian Sharpnose Shark (*Rhizoprionodon lalandii*). First, it is important to note how these organisms are exposed to COC in their natural habitat, the Sernambetiba channel. Levels of COC of 23.0 μg Kg^{-1} were detected in the samples, which are three time higher than the levels of BE, which amount to 7.0 μg Kg^{-1}. Specifically, higher concentrations of COC were detected in muscle (33.8 ± 33.4 μg Kg^{-1}) than in the liver (12.2 ± 14.2 μg Kg^{-1}). The results obtained by de Farias Araujo et al. [73] highlighted a tendency for COC and BE accumulation that differed between the sexes, even though the species does not exhibit sexual segregation during its life cycle. COC levels were found to be

higher in the muscle tissue of female (40.2 ± 35.8 μg Kg^{-1}) than in males (12.4 ± 5.9 μg Kg^{-1}). Instead, males and females might have been in different life stages: it was observed that all males were juvenile, while most females were adults. For this reason, these organisms tend to exhibit different metabolic rates and distinct physiological pathways, as found by Festa et al. [161] in other vertebrates of different species. Specifically, juvenile sharks present elevated metabolic rates compared to adults, while adult females possess more efficient detoxification systems, having been exposed to environmental conditions for a longer period. Obviously, all these factors influence the way in which contaminants are metabolized and stored. Furthermore, differences were found between pregnant and non-pregnant females regarding the metabolic processes that occur between these life stages. Pregnant sharks undergo physiological changes and greater metabolic demands to support embryo growth and development. This could influence the efficiency of detoxification processes, leading to variation in the contaminant metabolism and their distribution and accumulation [162], compared to what is observed in non-pregnant individuals.

The revelation of these substances in major marine predators, such as sharks, indicates that COC has now spread globally. Consequently, concerns are increasingly growing regarding the direct effects that COC could cause in marine food webs and the resulting negative consequences [163]. Indeed, the presence of illicit drugs in marine fauna constitutes a potential risk for these species, which may experience physiological stress following the alteration of biochemical functions [70], influencing growth, reproduction, and health, with the potential to alter the behaviour of marine organisms [71]. This could also influence feeding and mating processes, as well as the avoidance strategies of predators, which in the long term could cause a loss of biodiversity. The result would be the alteration of ecological interactions and the destruction of the balance of aquatic ecosystems [72], which are increasingly under pressure from anthropogenic activities.

Furthermore, in the context of public health, biomagnification is becoming an increasing concern, due to the accumulation of COC even in the highest trophic levels, as evidenced by the studies conducted by de Farias Araujo et al. [73]. Indeed, the presence of COC could indirectly impact fish stocks which would no longer be considered safe food products, and consequently, this could have significant ecological, economic, and social impacts [163].

5. Conclusions

The presence of COC and its main metabolites in aquatic environments is now a growing ecotoxicological and health issue, in fact, it is now included in the list of emerging contaminants. Growing interest in this class of pollutants has prompted numerous researchers in recent years to investigate their distribution across different geographic regions and environmental matrices, including surface waters, wastewater effluents, and sediments, as well as the physiological, behavioural, and reproductive effects of COC and its main metabolites on exposed organisms. The most observed effects in the range of environmental concentrations from 0.13 ng/L to 537 ng/L include oxidative stress, endocrine dysfunction, behavioural changes, and impaired reproductive capacity which represent the main ecotoxicological endpoints of exposure. Despite this, the actual extent of the environmental load may be underestimated, as most monitoring studies focus on aquatic matrices, neglecting sediments and organisms, which are key compartments for long-term persistence and bioaccumulation. Furthermore, the high spatial and temporal variability of concentrations affected by population density, treatment system efficiency, and seasonal consumption patterns makes accurate characterization of environmental exposure complex. However, despite the extensive literature available, some significant issues have emerged. Firstly, many studies have been conducted under laboratory conditions, without taking into account the possible interactions of COC and its metabolites with other xenobiotics, thus limiting the ecological transferability of the results. In natural environment, in fact, COC coexists with numerous other substances (pharmaceuticals, pesticides, microplastics), and the main gaps in our knowledge. In addition, there is a discrepancy between environmental concentrations and those used in experimental studies: may laboratory investigations employ exposure levels significantly higher than real-world conditions, compromising ecological relevance and potentially overestimating risk if not integrated with studies conducted under realistic and chronic exposure scenarios. Available evidence also indicates that sensitivity to COC is strongly species-specific and dependent on developmental stage, with early life stages such as embryos and larvae generally being more vulnerable than adults, likely due to immature detoxification systems and higher metabolic rates. Model organisms such as *Daphnia magna* have shown effects on mobility and reproduction, while in fish neurobehavioral and physiological alterations have been observed, attributable to the interaction of COC with neurotransmitter systems. However, the limited number of species studied and lack of standardized protocols reduce the generalizability of these findings. One of the main gaps concerns the difficulty of translating effects observed at the individual level into concrete ecological implications: although physiological

and behavioural alterations are well documented, their impact on populations and ecosystems remains largely speculative. Seemingly minor behavioural changes may trigger cascading effects, influencing trophic interactions and energy flow in aquatic ecosystems; similarly, reproductive effects could affect population dynamics over the long term, especially under chronic exposure conditions. Therefore, the gap between experimental conditions and real-world scenarios represents one of the main challenges in assessing the environmental risk of COC. Natural ecosystems are characterized by chronic exposures, fluctuating concentrations, multiple stressors, and complex biological interactions factors rarely reproduced in laboratory setting. To improve ecological relevance, future studies should use realistic concentrations, consider long-term exposure, evaluate mixture toxicity, integrate multiple biological levels, and adopt more complex approaches such as mesocosm and field studies, along with the development of predictive models. Ultimately, the central issue is not only whether COC can induce toxic effects, but whether these effects translate into significant ecological risk may be limited. However, this conclusion must be interpreted with caution, considering the continuous release of the substance into aquatic environments, its potential persistence, and interactions with other contaminants, which may result in chronic exposures with cumulative effects that are potentially underestimated. In light of these considerations, future research should prioritise chronic exposure at environmental concentrations, investigate the effects of contaminant mixtures, integrate molecular biomarkers, and develop predictive models to assess long-term risk. Moreover, it is essential to expand knowledge on the bioaccumulation of COC; preliminary evidence, including observations in apex predators sush as *Rhizoprionodon lalandii*, suggests possible transfer along the trophic network, although the extent of biomagnification and its impact on ecosystems and human health remain uncertain. In this context, it is essential to encourage interdisciplinary studies that integrate ecotoxicology, environmental chemistry, physiology, and ethology. Only through a holistic and preventive approach will it be possible to fully assess the ecological and health consequences of this contaminant. For example, using the Wastewater-Based Epidemiology (WBE) approach for wastewater monitoring, it is possible to identify areas with high levels of COC, where human consumption is the primary source of environmental contamination. Furthermore, the accuracy of this approach is ensured by the analytical method like LC-MS, which enables the detection of tiny quantities of analytes (in the range of ng/L and μg/L) even in billions of litres of water. This tool allows health authorities to implement targeted prevention strategies aimed at reducing the chemical load that is indirectly introduced into aquatic ecosystems. In this context, it would be advisable to launch public information campaigns to raise awareness of the environmental risks associated with the use of illicit drugs, highlighting how these substances can compromise the health of organisms and the stability of the food web. However, technological upgrading of WWTPS remains essential, as many current facilities are not designed to eliminate these specific contaminants. Furthermore, as not all emerging contaminants are routinely monitored, it would be advisable to make monitoring mandatory and to establish legal limits for the concentrations of COC and its metabolites in surface waters in order to ensure a long-term protection of aquatic biodiversity.

Author Contributions

C.R.M: Writing—original draft, Writing—review and editing, Resources, Visualization. S.F.: Writing—original draft, Writing—review and editing, Resources, Methodology, Data curation. G.S.: Writing—original draft, Writing—review and editing, Resources, Methodology, Data curation. D.B.: Writing—review and editing, Supervision. G.P.: Writing—review and editing. N.S.: Writing—review and editing. F.I.: Resources. C.F.: Supervision, Project administration, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest. Given the role as Editor-in-Chief, Damià Barceló had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. Sharma, D.; Sinha, R.; Multisanti, C.R.; et al. From personal hygiene products to health threats: Triclosan and its impact on endocrine health. *Sci. Total Environ.* **2025**, *1006*, 180856.
2. Zicarelli, G.; Pastorino, P.; Mossotto, C.; et al. Hidden Hazard: The detrimental effect of personal care products on amphibian species. *Aquat. Toxicol.* **2025**, *289*, 107603.
3. Bayrak, M.; Yüce, P.A.; Günal, A.Ç.; et al. Physiological and histopathological response of non-target organisms to emamectin benzoate: An effective innovative insecticide or a new ecosystem health hazard? *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2025**, *296*, 110241.
4. Meena, V.; Swami, D.; Chandel, A.; et al. Selected emerging contaminants in water: Global occurrence, existing treatment technologies, regulations and associated risk. *J. Hazard. Mater.* **2025**, *483*, 136541.
5. Morin-Crini, N.; Lichtfouse, E.; Liu, G.; et al. Emerging contaminants: Analysis, aquatic compartments and water pollution. In *Emerging Contaminants Vol. 1. Environmental Chemistry for a Sustainable World*; Springer: Cham, Switzerland, 2021.
6. Morin-Crini, N.; Lichtfouse, E.; Liu, G.; et al. Worldwide cases of water pollution by emerging contaminants: A review. *Environ. Chem. Lett.* **2022**, *20*, 2311–2338.
7. Noguera-Oviedo, K.; Aga, D.S. Lessons learned from more than two decades of research on emerging contaminants in the environment. *J. Hazard. Mater.* **2016**, *316*, 242–251.
8. Fontes, M.K.; Maranho, L.A.; Pereira, C.D.S. Review on the occurrence and biological effects of illicit drugs in aquatic ecosystems. *Environ. Sci. Pollut. Res.* **2020**, *27*, 30998–31034.
9. Impellitteri, F.; Multisanti, C.R.; Rusanova, P.; et al. Exploring the impact of contaminants of emerging concern on fish and invertebrates physiology in the Mediterranean Sea. *Biology* **2023**, *12*, 767.
10. Barathinivas, A.; Ramya, S.; Neethirajan, K.; et al. Ecotoxicological effects of pesticides on hematological parameters and oxidative enzymes in freshwater Catfish, *Mystus keletius*. *Sustainability* **2022**, *14*, 9529.
11. Caferro, A.; Iovine, M.A.; Impellitteri, F.; et al. Morphological and functional response of *Mytilus galloprovincialis* exposed to the Enalapril metabolite, Enalaprilat. *Environ. Toxicol. Pharmacol.* **2025**, *117*, 104746.
12. Sehonova, P.; Plhalova, L.; Blahova, J.; et al. Effects of selected tricyclic antidepressants on early-life stages of common carp (*Cyprinus carpio*). *Chemosphere* **2017**, *185*, 1072–1080.
13. Multisanti, C.R.; Zicarelli, G.; Caferro, A.; et al. Personal care products as a potential source of aquatic pollution: Effect of polyvinyl alcohol on physiological and antioxidant responses in *Mytilus galloprovincialis*. *Ecotoxicol. Environ. Saf.* **2025**, *298*, 118336.
14. Zicarelli, G.; Multisanti, C.R.; Falco, F.; et al. Evaluation of toxicity of Personal Care Products (PCPs) in freshwaters: Zebrafish as a model. *Environ. Toxicol. Pharmacol.* **2022**, *94*, 103923.
15. Carrizo, J.C.; Duy, S.V.; Munoz, G.; et al. Suspect screening of pharmaceuticals, illicit drugs, pesticides, and other emerging contaminants in Argentinean *Piaractus mesopotamicus*, a fish species used for local consumption and export. *Chemosphere* **2022**, *309*, 136769.
16. Impellitteri, F.; Yunko, K.; Martyniuk, V.; et al. Physiological and biochemical responses to caffeine and microplastics in *Mytilus galloprovincialis*. *Sci. Total Environ.* **2023**, *890*, 164075.
17. Akhilghosh, K.A.; Ramesh, A.; Aiswriya, V.P.; et al. Prevalence of emerging contaminants in the outlet of sewage treatment plants: An evidential report from Kerala, India with future concerns. *Environ. Sustain.* **2026**, 1–16. https://doi.org/10.1007/s42398-026-00421-y.
18. Kannan, M.; Bojan, N.; Swaminathan, J.; et al. Nanopesticides in agricultural pest management and their environmental risks: A review. *Int. J. Environ. Sci. Technol.* **2023**, *20*, 10507–10532.
19. Bodus, B.; O'Malley, K.; Dieter, G.; et al. Review of emerging contaminants in green stormwater infrastructure: Antibiotic resistance genes, microplastics, tire wear particles, PFAS, and temperature. *Sci. Total Environ.* **2024**, *906*, 167195.
20. Baker, D.R.; Očenášková, V.; Kvicalova, M.; et al. Drugs of abuse in wastewater and suspended particulate matter—Further developments in sewage epidemiology. *Environ. Int.* **2012**, *48*, 28–38.

21. Daughton, C.G. Illicit drugs and the environment. In *Illicit Drugs in the Environment: Occurrence, Analysis, and Fate Using Mass Spectrometry*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2011; pp. 1–27.
22. Campestrini, I.; Jardim, W.F. Occurrence of cocaine and benzoylecgonine in drinking and source water in the São Paulo State region, Brazil. *Sci. Total Environ.* **2017**, *576*, 374–380.
23. Bijekar, S.; Padariya, H.D.; Yadav, V.K.; et al. The state of the art and emerging trends in the wastewater treatment in developing nations. *Water* **2022**, *14*, 2537.
24. Pereira, C.D.S.; Maranho, L.A.; Cortez, F.S.; et al. Occurrence of pharmaceuticals and cocaine in a Brazilian coastal zone. *Sci. Total Environ.* **2016**, *548*, 148–154.
25. Fijalkowski, K. Emerging contaminants in sludge (endocrine disruptors, pesticides, and pharmaceutical residues, including illicit drugs/controlled substances, etc.). In *Industrial and Municipal Sludge*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 455–473.
26. Rosi-Marshall, E.J.; Snow, D.; Bartelt-Hunt, S.L.; et al. A review of ecological effects and environmental fate of illicit drugs in aquatic ecosystems. *J. Hazard. Mater.* **2015**, *282*, 18–25.
27. Sodré, F.F.; Freire, D.D.J.S.; Alcântara, D.B.; et al. Understanding illicit drug use trends during the Carnival holiday in the Brazilian capital through wastewater analysis. *Front. Anal. Sci.* **2022**, *2*, 930480.
28. Roveri, V.; Guimarães, L.L.; Kiyotani, R.B.; et al. Temporal variability and ecological risks of pharmaceuticals and cocaine during the Christmas and New Year holidays in a beach area of North Coast of São Paulo, Brazil. *Mar. Environ. Res.* **2024**, *202*, 106759.
29. Rousis, N.; Bade, R.; Romero-Sánchez, I.; et al. Festivals following the easing of COVID-19 restrictions: Prevalence of new psychoactive substances and illicit drugs. *Environ. Int.* **2023**, *178*, 108075.
30. González-Alonso, S.; Merino, L.M.; Esteban, S.; et al. Occurrence of pharmaceutical, recreational and psychotropic drug residues in surface water on the northern Antarctic Peninsula region. *Environ. Pollut.* **2017**, *229*, 241–254.
31. Castiglioni, S.; Zuccato, E. Illicit drugs as emerging contaminants. In *Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations*; American Chemical Society: Washington, DC, USA, 2010; Chapter 5, pp. 119–136.
32. Zhao, J.; Lu, J.; Zhao, H.; et al. Illicit drugs and their metabolites in urban wastewater: Analysis, occurrence and consumption in Xinjiang, China. *Sci. Total Environ.* **2022**, *852*, 158457.
33. Melones-Peña, N.; Maroto-Melle, E.C.; Torrado-Del Rey, S.; et al. Ecotoxicological risk and seasonal removal of licit and illicit drugs in wastewater treatment plants: A comparison of secondary and tertiary processes. *J. Hazard. Mater.* **2025**, *499*, 140290.
34. Pisetta, A.M.; Roveri, V.; Guimarães, L.L.; et al. First report on the occurrence of pharmaceuticals and cocaine in the coastal waters of Santa Catarina, Brazil, and its related ecological risk assessment. *Environ. Sci. Pollut. Res.* **2022**, *29*, 63099–63111.
35. Jones-Lepp, T.L.; Alvarez, D.A.; Petty, J.D.; et al. Polar organic chemical integrative sampling and liquid chromatography–electrospray/ion-trap mass spectrometry for assessing selected prescription and illicit drugs in treated sewage effluents. *Arch. Environ. Contam. Toxicol.* **2004**, *47*, 427–439.
36. Zuccato, E.; Chiabrando, C.; Castiglioni, S.; et al. Cocaine in surface waters: A new evidence-based tool to monitor community drug abuse. *Environ. Health* **2005**, *4*, 14.
37. Pal, R.; Megharaj, M.; Kirkbride, K.P.; et al. Illicit drugs and the environment—A review. *Sci. Total Environ.* **2013**, *463*, 1079–1092.
38. Evgenidou, E.N.; Konstantinou, I.K.; Lambropoulou, D.A. Occurrence and removal of transformation products of PPCPs and illicit drugs in wastewaters: A review. *Sci. Total Environ.* **2015**, *505*, 905–926.
39. Devault, D.A.; Lévi, Y.; Karolak, S. Applying sewage epidemiology approach to estimate illicit drug consumption in a tropical context: Bias related to sewage temperature and pH. *Sci. Total Environ.* **2017**, *584*, 252–258.
40. Mastroianni, N.; Bleda, M.J.; de Alda, M.L.; et al. Occurrence of drugs of abuse in surface water from four Spanish river basins: Spatial and temporal variations and environmental risk assessment. *J. Hazard. Mater.* **2016**, *316*, 134–142.
41. Vazquez-Roig, P.; Blasco, C.; Picó, Y. Advances in the analysis of legal and illegal drugs in the aquatic environment. *TrAC Trends Anal. Chem.* **2013**, *50*, 65–77.
42. Binelli, A.; Marisa, I.; Fedorova, M.; et al. First evidence of protein profile alteration due to the main cocaine metabolite (benzoylecgonine) in a freshwater biological model. *Aquat. Toxicol.* **2013**, *140*, 268–278.
43. Drake, L.R.; Scott, P.J. DARK classics in chemical neuroscience: Cocaine. *ACS Chem. Neurosci.* **2018**, *9*, 2358–2372.
44. Torchetti, T. Coca chewing and high altitude adaptation. *UWOJA* **1994**, *1*, 95–98.
45. Biondich, A.S.; Joslin, J.D. Coca: The history and medical significance of an ancient Andean tradition. *Emerg. Med. Int.* **2016**, *1*, 4048764.
46. Karch, S.B. *A Brief History of Cocaine*, 2nd ed.; Routledge: New York, NY, USA, 2017.

47. Cisneros, O.; de de Jesus, K.G.; Then, E.O.; et al. Bilateral basal ganglia infarction after intranasal use of cocaine: A case report. *Cureus* **2019**, *11*, e4405.
48. Cosenza, M.; Panza, L.; Califano, A.P.; et al. Carotid thrombosis in a crack cocaine smoker woman. *Case Rep. Vasc. Med.* **2020**, *1*, 4894825.
49. Vermeulen, L.; Dirix, M.; Dendooven, A. Cocaine Consumption and Antineutrophil Cytoplasmic Antibody–associated Glomerulonephritis: A Case Report. *Am. J. Forensic Med. Pathol.* **2021**, *42*, 198–200.
50. Redman, M. Cocaine: What is the crack? A brief history of the use of cocaine as an anesthetic. *Anesthesiol. Pain Med.* **2011**, *1*, 95–97.
51. Heard, K.; Palmer, R.; Zahniser, N.R. Mechanisms of acute cocaine toxicity. *Open Pharmacol. J.* **2008**, *2*, 70.
52. Grilly, D.M.; Salamone, J. *Drugs, Brain, and Behavior*, 6th ed.; Pearson: Boston, MA, USA, 2011.
53. United Nation. World Drug Report 2025. Available online: https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2025.html (accessed on 10 December 2025).
54. Bravo, R.R.; Faria, A.C.; Brito-da-Costa, A.M.; et al. Cocaine: An updated overview on chemistry, detection, biokinetics, and pharmacotoxicological aspects including abuse pattern. *Toxins* **2022**, *14*, 278.
55. Volkow, N.D.; Wang, G.J.; Fischman, M.W.; et al. Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. *Life Sci.* **2000**, *67*, 1507–1515.
56. Huang, Y.; Xie, X.; Zhou, L.J.; et al. Multi-phase distribution and risk assessment of endocrine disrupting chemicals in the surface water of the Shaying River-Huai River Basin, China. *Ecotoxicol. Environ. Saf.* **2019**, *173*, 45–53.
57. Hedgespeth, M.L.; Gibson, N.; McCord, J.; et al. Suspect screening and prioritization of chemicals of concern (COCs) in a forest-water reuse system watershed. *Sci. Total Environ.* **2019**, *694*, 133378.
58. van Nuijs, A.L.; Pecceu, B.; Theunis, L.; et al. Spatial and temporal variations in the occurrence of cocaine and benzoylecgonine in waste- and surface water from Belgium and removal during wastewater treatment. *Water Res.* **2009**, *43*, 1341–1349.
59. Zhang, Y.; Zhang, T.; Guo, C.; et al. Drugs of abuse and their metabolites in the urban rivers of Beijing, China: Occurrence, distribution, and potential environmental risk. *Sci. Total Environ.* **2017**, *579*, 305–313.
60. Thomas, K.V.; Da Silva, F.M.A.; Langford, K.H.; et al. Screening for selected human pharmaceuticals and cocaine in the urban streams of Manaus, Amazonas, Brazil. *JAWRA* **2014**, *50*, 302–308.
61. Roveri, V.; Guimarães, L.L.; Toma, W.; et al. Occurrence of pharmaceuticals and cocaine in the urban drainage channels located on the outskirts of the São Vicente Island (São Paulo, Brazil) and related ecological risk assessment. *Environ. Sci. Pollut. Res.* **2022**, *29*, 57931–57945.
62. Klosterhaus, S.L.; Grace, R.; Hamilton, M.C.; et al. Method validation and reconnaissance of pharmaceuticals, personal care products, and alkylphenols in surface waters, sediments, and mussels in an urban estuary. *Environ. Int.* **2013**, *54*, 92–99.
63. Castiglioni, S.; Davoli, E.; Riva, F.; et al. Data on occurrence and fate of emerging contaminants in a urbanised area. *Data Brief* **2018**, *17*, 533–543.
64. Fontes, M.K.; de Campos, B.G.; Cortez, F.S.; et al. Seasonal monitoring of cocaine and benzoylecgonine in a subtropical coastal zone (Santos Bay, Brazil). *Mar. Pollut. Bull.* **2019**, *149*, 110545.
65. López, H.M. Footprints of cocaine: a bibliometric analysis and systematic review of the environmental impacts of the cocaine value chain in Latin America. *Environ. Res. Lett*. **2025**, *20*, 033002.
66. Acosta Garcia, N. Catching the White Fish: Gossip and cocaine on Colombia's Northern Pacific coast. *JRAI* **2021**, *27*, 128–145.
67. Binelli, A.; Pedriali, A.; Riva, C.; et al. Illicit drugs as new environmental pollutants: Cyto-genotoxic effects of cocaine on the biological model *Dreissena polymorpha*. *Chemosphere* **2012**, *86*, 906–911.
68. Capaldo, A.; Gay, F.; Lepretti, M.; et al. Effects of environmental cocaine concentrations on the skeletal muscle of the European eel (*Anguilla anguilla*). *Sci. Total Environ.* **2018**, *640*, 862–873.
69. Bijlsma, L.; Boix, C.; Niessen, W.M.; et al. Investigation of degradation products of cocaine and benzoylecgonine in the aquatic environment. *Sci. Total Environ.* **2013**, *443*, 200–208.
70. dos Santos Barbosa Ortega, A.; Maranho, L.A.; Nobre, C.R.; et al. Detoxification, oxidative stress, and cytogenotoxicity of crack cocaine in the brown mussel *Perna perna*. *Environ. Sci. Pollut. Res.* **2019**, *26*, 27569–27578.
71. De Felice, B.; Salgueiro-González, N.; Castiglioni, S.; et al. Biochemical and behavioral effects induced by cocaine exposure to *Daphnia magna*. *Sci. Total Environ.* **2019**, *689*, 141–148.
72. Nowicki, R.J.; Thomson, J.A.; Fourqurean, J.W.; et al. Loss of predation risk from apex predators can exacerbate marine tropicalization caused by extreme climatic events. *J. Anim. Ecol.* **2021**, *90*, 2041–2052.
73. de Farias Araujo, G.; Medeiros, R.J.; Maciel-Magalhães, M.; et al. Zebrafish (*Danio rerio*) as a model to assess the effects of cocaine as a drug of abuse and its environmental implications. *Environ. Sci. Pollut. Res.* **2023**, *30*, 28459–28479.

74. da Silva Souza, L.; Pusceddu, F.H.; Cortez, F.S.; et al. Harmful effects of cocaine byproduct in the reproduction of sea urchin in different ocean acidification scenarios. *Chemosphere* **2019**, *236*, 124284.
75. de Farias Araujo, G.; de Oliveira, L.V.A.; Hoff, R.B.; et al. "Cocaine Shark": First report on cocaine and benzoylecgonine detection in sharks. *Sci. Total Environ.* **2024**, *948*, 174798.
76. Parolini, M.; Ghilardi, A.; Della Torre, C.; et al. Environmental concentrations of cocaine and its main metabolites modulated antioxidant response and caused cyto-genotoxic effects in zebrafish embryo cells. *Environ. Pollut.* **2017**, *226*, 504–514.
77. Kovacic, P.; Ames, J.R.; Jawdosiuk, M.; Ryan, M.D. Electron transfer mechanism for cocaine action. In *Redox Chemistry and Interfacial Behavior of Biological Molecules*; Dryhurst, G., Niki, K., Eds.; Springer: Boston, MA, USA, 1988; pp. 323–331.
78. Kovacic, P. Role of oxidative metabolites of cocaine in toxicity and addiction: Oxidative stress and electron transfer. *Med. Hypotheses* **2005**, *64*, 350–356.
79. Kloss, M.W.; Rosen, G.M.; Rauckman, E.J. Biotransformation of norcocaine to norcocaine nitroxide by rat brain microsomes. *Psychopharmacology* **1984**, *84*, 221–224.
80. Lloyd, R.V.; Shuster, L.; Mason, R.P. Reexamination of the microsomal transformation of *N*-hydroxynorcocaine to norcocaine nitroxide. *Mol. Pharmacol.* **1993**, *43*, 645–648.
81. Kloss, M.W.; Rosen, G.M.; Rauckman, E.J. Evidence of enhanced *in vivo* lipid peroxidation after acute cocaine administration. *Toxicol. Lett.* **1983**, *15*, 65–70.
82. Gutteridge, J. Lipid peroxidation and antioxidants as biomarkers of tissue damage. *Clin. Chem.* **1995**, *41*, 1819–1828.
83. Multisanti, C.R.; Ferrara, S.; Piccione, G.; et al. Plastics and their derivatives are impacting animal ecophysiology: A review. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2025**, *291*, 110149.
84. Multisanti, C.R.; Rizzo, M.G.; Impellitteri, F.; et al. Evaluation of physiological changes in *Mytilus galloprovincialis* exposed to an isothiazolinone-based compound: A multi-marker approach. *Ecotoxicol. Environ. Saf.* **2025**, *308*, 119508.
85. Impellitteri, F.; Multisanti, C.R.; Di Paola, D.; et al. A Comparative Analysis of Physiological and Morphological Alteration in *Mytilus galloprovincialis* After Exposure to Polyethylene Glycol (PEG). *Microsc. Res. Tech.* **2025**, *88*, 2222–2231.
86. Martyniuk, V.; Matskiv, T.; Yunko, K.; et al. Reductive stress and cytotoxicity in the swollen river mussel (*Unio tumidus*) exposed to microplastics and salinomycin. *Environ. Pollut.* **2024**, *350*, 123724.
87. Freitas, R.; Silvestro, S.; Pagano, M.; et al. Impacts of salicylic acid in *Mytilus galloprovincialis* exposed to warming conditions. *Environ. Toxicol. Pharmacol.* **2020**, *80*, 103448.
88. Tresnakova, N.; Famulari, S.; Zicarelli, G.; et al. Multi-characteristic toxicity of enantioselective chiral fungicide tebuconazole to a model organism Mediterranean mussel *Mytilus galloprovincialis* Lamarck, 1819 (Bivalve: Mytilidae). *Sci. Total Environ.* **2023**, *862*, 160874.
89. Fontes, M.K.; Dourado, P.L.R.; de Campos, B.G.; et al. Environmentally realistic concentrations of cocaine in seawater disturbed neuroendocrine parameters and energy status in the marine mussel *Perna perna*. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2022**, *251*, 109198.
90. Ricciardi, F.; Binelli, A.; Provini, A. Use of two biomarkers (CYP450 and acetylcholinesterase) in zebra mussel for the biomonitoring of Lake Maggiore (northern Italy). *Ecotoxicol. Environ. Saf.* **2006**, *63*, 406–412.
91. Ferreira-Vieira, T.; Guimaraes, I.M.; Silva, F.R.; et al. Alzheimer's disease: Targeting the cholinergic system. *Curr. Neuropharmacol.* **2016**, *14*, 101–115.
92. Rickwood, C.J.; Galloway, T.S. Acetylcholinesterase inhibition as a biomarker of adverse effect: A study of *Mytilus edulis* exposed to the priority pollutant chlorfenvinphos. *Aquat. Toxicol.* **2004**, *67*, 45–56.
93. Gagné, F.; André, C.; Gélinas, M. Neurochemical effects of benzodiazepine and morphine on freshwater mussels. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2010**, *152*, 207–214.
94. Fontes, M.K.; de Campos, B.G.; Cortez, F.S.; et al. Mussels get higher: A study on the occurrence of cocaine and benzoylecgonine in seawater, sediment and mussels from a subtropical ecosystem (Santos Bay, Brazil). *Sci. Total Environ.* **2021**, *757*, 143808.
95. Bacqué-Cazenave, J.; Bharatiya, R.; Barrière, G.; et al. Serotonin in animal cognition and behavior. *Int. J. Mol. Sci.* **2020**, *21*, 1649.
96. Cubero-Leon, E.; Ciocan, C.M.; Hill, E.M.; et al. Estrogens disrupt serotonin receptor and cyclooxygenase mRNA expression in the gonads of mussels (*Mytilus edulis*). *Aquat. Toxicol.* **2010**, *98*, 178–187.
97. Beiras, R.; Widdows, J. Effect of the neurotransmitters dopamine, serotonin and norepinephrine on the ciliary activity of mussel (*Mytilus edulis*) larvae. *Mar. Biol.* **1995**, *122*, 597–603.
98. De Felice, B.; Parolini, M. Effects of single and combined exposure to cocaine and benzoylecgonine on the oxidative status of *Mytilus galloprovincialis*. *Environ. Toxicol. Pharmacol.* **2020**, *80*, 103475.

99. de Oliveira David, J.A.; Salaroli, R.B.; Fontanetti, C.S. The significance of changes in *Mytella falcata* (Orbigny, 1842) gill filaments chronically exposed to polluted environments. *Micron* **2008**, *39*, 1293–1299.
100. Livingston, D.R.; Förlin, L.; George, S.G. Molecular biomarkers and toxic consequences of impact by organic pollution in aquatic organisms. In *Water Quality and Stress Indicators in Marine and Freshwater Systems: Linking Levels of Organization*; Freshwater Biological Association: Ambleside, UK, 1994.
101. Martyniuk, V.; Khoma, V.; Matskiv, T.; et al. Combined effect of microplastic, salinomycin and heating on *Unio tumidus*. *Environ. Toxicol. Pharmacol.* **2023**, *98*, 104068.
102. Lushchak, V.I. Environmentally induced oxidative stress in aquatic animals. *Aquat. Toxicol.* **2011**, *101*, 13–30.
103. Wang, X.; Yang, H.; Liu, G.; et al. Enzyme responses and lipid peroxidation in gills and hepatopancreas of clam *Mactra vereformis* following cadmium exposure. *J. Oceanol. Limnol.* **2011**, *29*, 981–989.
104. Pereira, L.; Fernandes, M.N.; Martinez, C.B. Hematological and biochemical alterations in the fish *Prochilodus lineatus* caused by the herbicide clomazone. *Environ. Toxicol. Pharmacol.* **2013**, *36*, 1–8.
105. Gonzalez-Rey, M.; Bebianno, M.J. Effects of non-steroidal anti-inflammatory drug (NSAID) diclofenac exposure in mussel *Mytilus galloprovincialis*. *Aquat. Toxicol.* **2014**, *148*, 221–230.
106. Verlecar, X.N.; Jena, K.B.; Chainy, G.B.N. Modulation of antioxidant defences in digestive gland of *Perna viridis* (L.) on mercury exposures. *Chemosphere* **2008**, *71*, 1977–1985.
107. Vlahogianni, T.H.; Valavanidis, A. Heavy-metal effects on lipid peroxidation and antioxidant defence enzymes in mussels *Mytilus galloprovincialis*. *Chem. Ecol.* **2007**, *23*, 361–371.
108. Gwoździński, K.; Gonciarz, M.; Kilańczyk, E.; et al. Antioxidant enzyme activities and lipid peroxidation in *Mytilus galloprovincialis* from the French Mediterranean coast. *Oceanol. Hydrobiol. Stud.* **2010**, *39*, 33–43.
109. Khessiba, A.; Roméo, M.; Aïssa, P. Effects of some environmental parameters on catalase activity measured in the mussel (*Mytilus galloprovincialis*) exposed to lindane. *Environ. Pollut.* **2005**, *133*, 275–281.
110. Kappus, H. Lipid peroxidation: Mechanisms, analysis, enzymology and biological relevance. In *Oxidative Stress*; Elsevier: Amsterdam, The Netherlands, 1985; pp. 273–310.
111. Mistri, M.; Munari, C.; Pagnoni, A.; et al. Accumulation of trace metals in crayfish tissues: Is *Procambarus clarkii* a vector of pollutants in Po Delta inland waters? *Eur. Zool. J.* **2020**, *87*, 46–57.
112. De Felice, B.; De Pascalis, F.; Manenti, R.; et al. Differential biochemical and behavioral responses induced by cocaine and benzoylecgonine exposure to the red swamp crayfish *Procambarus clarkii*. *Sci. Total Environ.* **2022**, *844*, 157025.
113. Pereira, R.B.; Andrade, P.B.; Valentão, P. A comprehensive view of the neurotoxicity mechanisms of cocaine and ethanol. *Neurotox. Res.* **2015**, *28*, 253–267.
114. Parolini, M.; Bini, L.; Magni, S.; et al. Exposure to cocaine and its main metabolites altered the protein profile of zebrafish embryos. *Environ. Pollut.* **2018**, *232*, 603–614.
115. García-Cambero, J.P.; García-Cortés, H.; Valcárcel, Y.; et al. Environmental concentrations of the cocaine metabolite benzoylecgonine induced sublethal toxicity in the development of plants but not in a zebrafish embryo–larval model. *J. Hazard. Mater.* **2015**, *300*, 866–872.
116. Zahm, D.S.; Becker, M.L.; Freiman, A.J.; et al. Fos after single and repeated self-administration of cocaine and saline in the rat: Emphasis on the Basal forebrain and recalibration of expression. *Neuropsychopharmacology* **2010**, *35*, 445–463.
117. Singh, S.; Tiwari, R.K.; Pandey, R.S. Evaluation of acute toxicity of triazophos and deltamethrin and their inhibitory effect on AChE activity in *Channa punctatus*. *Toxicol. Rep.* **2018**, *5*, 85–89.
118. Vicentic, A.; Lakatos, A.; Kuhar, M.J. CART (cocaine- and amphetamine-regulated transcript) peptide receptors: Specific binding in AtT20 cells. *Eur. J. Pharmacol.* **2005**, *528*, 188–189.
119. Rasmussen, S.G.; Carroll, F.I.; Maresch, M.J.; et al. Biophysical characterization of the cocaine binding pocket in the serotonin transporter using a fluorescent cocaine analogue as a molecular reporter. *J. Biol. Chem.* **2001**, *276*, 4717–4723.
120. Parolini, M.; Binelli, A. Sub-lethal effects induced by a mixture of three non-steroidal anti-inflammatory drugs (NSAIDs) on the freshwater bivalve *Dreissena polymorpha*. *Ecotoxicology* **2012**, *21*, 379–392.
121. Diez-Fernandez, C.; Zaragoza, A.; Alvarez, A.M.; et al. Cocaine cytotoxicity in hepatocyte cultures from phenobarbital-induced rats: Involvement of reactive oxygen species and expression of antioxidant defense systems. *Biochem. Pharmacol.* **1999**, *58*, 797–806.
122. Neri, M.; Bello, S.; Pascale, N.; et al. The long way to objectify organ damage related to cocaine abuse: Oxidative stress is the main culprit. *Mini-Rev. Org. Chem.* **2013**, *10*, 373–383.
123. Capaldo, A.; Gay, F.; Caputo, I.; et al. Effects of environmental cocaine concentrations on COX and caspase-3 activity, GRP-78, ALT, CRP and blood glucose levels in the liver and kidney of the European eel (*Anguilla anguilla*). *Ecotoxicol. Environ. Saf.* **2021**, *208*, 111475.
124. Keltz, E.; Khan, F.Y.; Mann, G. Rhabdomyolysis. The role of diagnostic and prognostic factors. *Muscles Ligaments Tendons J.* **2014**, *3*, 303–312.

125. Brazeau, G.A.; McArdle, A.; Jackson, M.J. Effects of cocaine on leakage of creatine kinase from skeletal muscle: *In vitro* and *in vivo* studies in mice. *Life Sci.* **1995**, *57*, 1569–1578.
126. Ordway, G.A.; Garry, D.J. Myoglobin: An essential hemoprotein in striated muscle. *J. Exp. Biol.* **2004**, *207*, 3441–3446.
127. Khan, F.Y. Rhabdomyolysis: A review of the literature. *Neth. J. Med.* **2009**, *67*, 272–283.
128. Bernet, D.; Schmidt, H.; Meier, W.; et al. Histopathology in fish: Proposal for a protocol to assess aquatic pollution. *J. Fish Dis.* **1999**, *22*, 25–34.
129. Valente, M.J.; Henrique, R.; Vilas-Boas, V.; et al. Cocaine-induced kidney toxicity: An *in vitro* study using primary cultured human proximal tubular epithelial cells. *Arch. Toxicol.* **2012**, *86*, 249–261.
130. Hotamisligil, G.S. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* **2010**, *140*, 900–917.
131. Banaee, M. Physiological dysfunction in fish after insecticides exposure. In *Insecticides: Development of Safer and More Effective Technologies*; IntechOpen: London, UK, 2013.
132. Villaplana, C.R.A.; Andrés, M.C.; Collado, J.T.R.; et al. Hyperglycemia secondary to consumption of cocaine and atypical antipsychotic drugs. *Endocrinol. Nutr.* **2008**, *55*, 372–375. https://doi.org/10.1016/S1575-0922(08)72799-2.
133. Gay, F.; Maddaloni, M.; Valiante, S.; et al. Endocrine disruption in the European eel, *Anguilla anguilla*, exposed to an environmental cocaine concentration. *Water Air Soil Pollut.* **2013**, *224*, 1579.
134. Kirla, K.T.; Groh, K.J.; Steuer, A.E.; et al. From the Cover: Zebrafish larvae are insensitive to stimulation by cocaine: Importance of exposure route and toxicokinetics. *Toxicol. Sci.* **2016**, *154*, 183–193. https://doi.org/10.1093/toxsci/kfw156.
135. Gholamhosseini, A.; Banaee, M.; Sureda, A.; et al. Physiological response of freshwater crayfish, *Astacus leptodactylus* exposed to polyethylene microplastics at different temperature. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2023**, *267*, 109581.
136. Subedi, B.; Anderson, S.; Croft, T.L.; et al. Gene alteration in zebrafish exposed to a mixture of substances of abuse. *Environ. Pollut.* **2021**, *278*, 116777.
137. Mech, A.M.; Merteroglu, M.; Sealy, I.M.; et al. Behavioral and gene regulatory responses to developmental drug exposures in zebrafish. *Front. Psychiatry* **2022**, *12*, 795175.
138. Mello, F.V.; Cunha, S.C.; Fogaça, F.H.; et al. Occurrence of pharmaceuticals in seafood from two Brazilian coastal areas: Implication for human risk assessment. *Sci. Total Environ.* **2022**, *803*, 149744.
139. Fontes, M.K.; Rosati, L.; Di Lorenzo, M.; et al. Aquatic pollution and risks to biodiversity: The example of cocaine effects on the ovaries of *Anguilla anguilla*. *Animals* **2022**, *12*, 1766.
140. Almeida, E.A.; Bainy, A.C.; Medeiros, M.H.; et al. Effects of trace metal and exposure to air on serotonin and dopamine levels in tissues of the mussel *Perna perna*. *Mar. Pollut. Bull.* **2003**, *46*, 1485–1490.
141. El-Bizri, H.; Guest, I.; Varma, D.R. Effects of cocaine on rat embryo development *in vivo* and in cultures. *Pediatr. Res.* **1991**, *29*, 187–190.
142. Mersereau, E.J.; Poitra, S.L.; Espinoza, A.; et al. The effects of cocaine on heart rate and electrocardiogram in zebrafish (*Danio rerio*). *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2015**, *172*, 1–6.
143. Barreto-Valer, K.; Lopez-Bellido, R.; Macho Sanchez-Simon, F.; et al. Modulation by cocaine of dopamine receptors through miRNA-133b in zebrafish embryos. *PLoS ONE* **2012**, *7*, e52701.
144. Falfushynska, H.; Rychter, P.; Boshtova, A.; et al. Illicit Drugs in Surface Waters: How to Get Fish off the Addictive Hook. *Pharmaceuticals* **2024**, *17*, 537.
145. del Carmen Gómez-Regalado, M.; Martín, J.; Santos, J.L.; et al. Bioaccumulation/bioconcentration of pharmaceutical active compounds in aquatic organisms: Assessment and factors database. *Sci. Total Environ.* **2023**, *861*, 160638.
146. Serra-Compte, A.; Maulvault, A.L.; Camacho, C.; et al. Effects of water warming and acidification on bioconcentration, metabolization and depuration of pharmaceuticals and endocrine disrupting compounds in marine mussels (*Mytilus galloprovincialis*). *Environ. Pollut.* **2018**, *236*, 824–834.
147. European Commission. *Commission Regulation (EU) No 253/2011 of 15 March 2011 Amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annex XIII*; European Commission: Brussels, Belgium, 2011.
148. Roveri, V.; Souza, U.P.; da Costa, J.H.A.; et al. Pharmaceuticals and cocaine in Brazilian seafood: an integrated weight-of-evidence assessment of bioaccumulation. *Reg. Stud. Mar. Sci.* **2026**, *96*, 104953.
149. Burgos-Aceves, M.A.; Faggio, C. An approach to the study of the immunity functions of bivalve haemocytes: physiology and molecular aspects. *Fish shellfish Immunol.* **2017**, *67*, 513–517.
150. Beyer, J.; Green, N.W.; Brooks, S.; et al. Blue mussels (*Mytilus edulis* spp.) as sentinel organisms in coastal pollution monitoring: A review. *Mar. Environ. Res.* **2017**, *130*, 338–365.
151. Miller, T.H.; Ng, K.T.; Bury, S.T.; et al. Biomonitoring of pesticides, pharmaceuticals and illicit drugs in a freshwater invertebrate to estimate toxic or effect pressure. *Environ. Int.* **2019**, *129*, 595–606.

152. Dodder, N.G.; Maruya, K.A.; Ferguson, P.L.; et al. Occurrence of contaminants of emerging concern in mussels (*Mytilus* spp.) along the California coast and the influence of land use, storm water discharge, and treated wastewater effluent. *Mar. Pollut. Bull.* **2014**, *81*, 340–346.
153. Roveri, V.; Souza, U.P.; da Costa, J.H.A.; et al. Occurrence of pharmaceuticals and cocaine in liver and muscle of different fish species from a Brazilian coastal zone. *Reg. Stud. Mar. Sci.* **2025**, *88*, 104266.
154. Maciel, T.R.; Vaz-dos-Santos, A.M.; Vianna, M. Can otoliths of *Genidens genidens* (Cuvier 1829) (Siluriformes: Ariidae) reveal differences in life strategies of males and females? *Environ. Biol. Fishes* **2018**, *101*, 1589–1598.
155. Capaldo, A.; Gay, F.; Maddaloni, M.; et al. Presence of cocaine in the tissues of the European eel, *Anguilla anguilla*, exposed to environmental cocaine concentrations. *Water Air Soil Pollut.* **2012**, *223*, 2137–2143.
156. Levisky, J.A.; Bowerman, D.L.; Jenkins, W.W.; et al. Drug deposition in adipose tissue and skin: Evidence for an alternative source of positive sweat patch tests. *Forensic Sci. Int.* **2000**, *110*, 35–46.
157. Nestler, E.J.; Malenka, R.C. The addicted brain. *Sci. Am.* **2004**, *290*, 78–85.
158. Hauser-Davis, R.A.; Rocha, R.C.C.; Saint'Pierre, T.D.; et al. Metal concentrations and metallothionein metal detoxification in blue sharks, *Prionace glauca* L. from the Western North Atlantic Ocean. *J. Trace Elem. Med. Biol.* **2021**, *68*, 126813.
159. Tiktak, G.P.; Butcher, D.; Lawrence, P.J.; et al. Are concentrations of pollutants in sharks, rays and skates (Elasmobranchii) a cause for concern? A systematic review. *Mar. Pollut. Bull.* **2020**, *160*, 111701.
160. Dulvy, N.K.; Pacoureau, N.; Rigby, C.L.; et al. Overfishing drives over one-third of all sharks and rays toward a global extinction crisis. *Curr. Biol.* **2021**, *31*, 4773–4787.
161. Festa, E.D.; Russo, S.J.; Gazi, F.M.; et al. Sex differences in cocaine-induced behavioral responses, pharmacokinetics, and monoamine levels. *Neuropharmacology* **2004**, *46*, 672–687.
162. Willmer, I.Q.; Wosnick, N.; Rocha, R.C.C.; et al. First report on metal and metalloid contamination of Ampullae of Lorenzini in sharks: A case study employing the Brazilian sharpnose shark *Rhizoprionodon lalandii* from Southeastern Brazil as an ecotoxicological model. *Mar. Pollut. Bull.* **2022**, *179*, 113671.
163. Hauser-Davis, R.A.; Wosnick, N.; Hoff, R.B.; et al. Cocaine and other illicit drugs in the marine environment: Potential effects and future directions. *Mar. Pollut. Bull.* **2024**, *208*, 117064.