



Review

Neurotoxicity of Benzotriazole Ultraviolet Stabilizers in Teleost Fishes: A Review

Mengli Li ^{1,†}, Emma Ivantsova ^{2,†} , Xuefang Liang ¹ and Christopher J. Martyniuk ^{2,*} 

¹ Inner Mongolia Key Laboratory of Environmental Pollution Control & Waste Resource Reuse, School of Ecology and Environment, Inner Mongolia University, Hohhot 010021, China; limengli0718@126.com (M.L.); liangxf@imu.edu.cn (X.L.)

² Department of Physiological Sciences and Center for Environmental and Human Toxicology, University of Florida Genetics Institute, Interdisciplinary Program in Biomedical Sciences Neuroscience, College of Veterinary Medicine, University of Florida, Gainesville, FL 32611, USA; eivantsova@ufl.edu

* Correspondence: cmartyn@ufl.edu

† These authors contributed equally to this work.

Abstract: Plastic additives that maintain integrity have been extensively studied for potential toxicity to fish; however, chemicals that protect polymers from (artificial) UV degradation are less studied. Benzotriazole UV stabilizers (BUVSs) are the most widely used UV stabilizers in plastics and are often used in sunscreens, cosmetics, paint, and food packaging. BUVSs can negatively affect aquatic wildlife when released into the environment via plastic degradation. In this review, we summarize the distribution of BUVSs globally and discuss neurotoxicological endpoints measured in fish to understand how these plastic additives can affect the neurological health of teleost fishes. BUVSs have been detected in aquatic environments at concentrations ranging from 0.05 up to 99,200 ng/L. Studies show that BUVSs affect behavioral responses and acetylcholinesterase activity, indicators of neurotoxicity. Our computational analysis using transcriptome data suggests certain pathways associated with neurodegeneration are responsive to exposure to BUVSs, like “Complement Activation in Alzheimer’s Disease”. Based on our review, we identify some research needs for future investigations: (1) molecular studies in the central nervous system to define precise mechanisms of neurotoxicity; (2) a wider range of tests for assessing aberrant behaviors given that BUVSs can affect the activity of larval zebrafish; and (3) histopathology of the nervous system to accompany biochemical analyses. These data are expected to enhance understanding of the neurotoxicity potential of benzotriazoles and other plastic additives.

Keywords: plasticizers; central nervous system; aquatic toxicology; BUVS; behavior; plastic additives



Citation: Li, M.; Ivantsova, E.; Liang, X.; Martyniuk, C.J. Neurotoxicity of Benzotriazole Ultraviolet Stabilizers in Teleost Fishes: A Review. *Toxics* **2024**, *12*, 125. <https://doi.org/10.3390/toxics12020125>

Academic Editor: Michael Caudle

Received: 23 December 2023

Revised: 23 January 2024

Accepted: 25 January 2024

Published: 2 February 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction: Ultraviolet Stabilizers, Non-Negligible Additives in Plastics

Microplastic pollution has received intensifying attention as an emerging worldwide environmental issue. One of the most important problems with microplastics is the leaching of harmful additives [1]. During plastic production, chemical additives are often added to improve the performance, functionality, and ageing properties of the polymer. Plastics often contain four types of plastic additives: plasticizers, flame retardants, light stabilizers, and antioxidants. Amongst these additives, plasticizers and flame retardants are the most frequently added, at a proportion of >70% to products. Plasticizers are functional additives that improve plasticity, flexibility, processability, and durability [2]. They are mostly used in polyvinyl chloride (PVC) products, but are also used in wires, cables, coatings, product packaging, cosmetics, pharmaceuticals, and medical devices [3–6]. Currently, there are over 500 types of plasticizers produced industrially. To protect plastics and plasticizers, other stabilizing chemicals are embedded in polymer resins to delay the overall oxidative degradation of plastics if/when exposed to ultraviolet (UV) light [7]. Although they only account for 0.05–3% of the number of additives used in plastic manufacturing, their

ubiquitous detection in the environment and biota, as well as potential toxicity to aquatic organisms, has led to increased concern regarding their aquatic ecosystem presence.

UV stabilizers are a group of substances that protect polymers from degradation caused by sunlight or other artificial UV light. Of these, benzotriazole derivatives are the most widely used UV stabilizers in plastics [8]. Benzotriazole UV stabilizers (BUVSs) share a common 2-hydroxyphenyl benzotriazole structure, and the derivatives are classified by various alkyl substitutions on the phenol ring (Figure 1). UVSs can absorb the full spectrum of UV light, including UV-A (320–400 nm) and UV-B light (280–320 nm), to prevent light-induced yellowing and degradation of products [9]. Due to these unique properties, benzotriazole UV stabilizers (BUVSs) are often used in sunscreen, cosmetics, and other personal care products [10–12], as well as in plastics, paints, and food packaging [13,14]. UVSs have been added to the list of high-production-volume (HPV) chemicals [15].

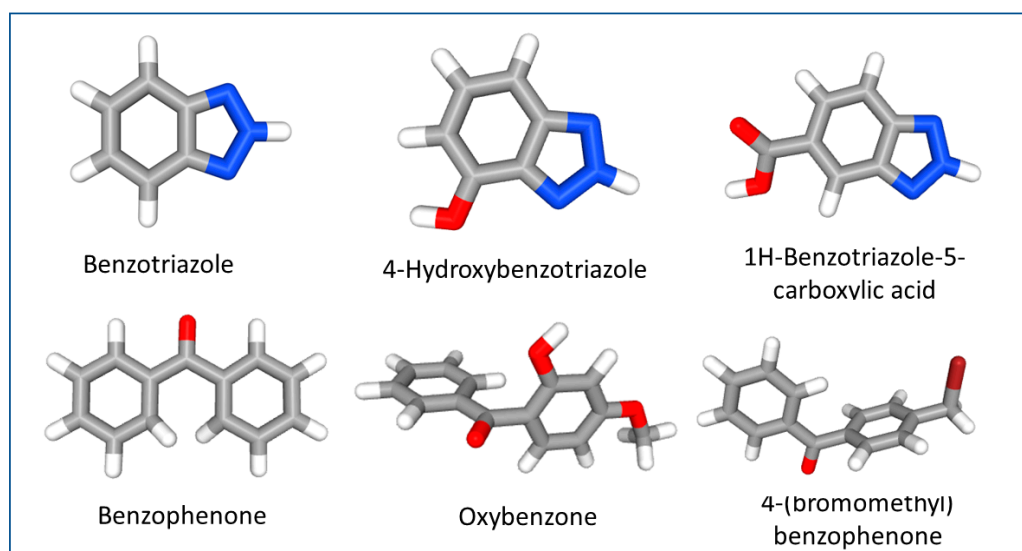


Figure 1. A 3D depiction of examples of different benzotriazoles, benzophenones, and their derivatives. Red indicates the position of oxygen, and blue indicates the position of nitrogen. Images extracted from the National Center for Biotechnology Information (2023). PubChem Compound Summary. Images retrieved 1 March 2023.

2. Objectives of the Review

The objectives of this review were to (1) summarize the distribution of UVSs on a global scale and (2) review studies in fish to better understand how these plastic additives may affect the neurological health of aquatic species. While exposure to UVSs can have a range of biological effects in fish, including oxidative stress, reproductive disruption, and immunotoxicity [16–18], we elect to focus here on neurotoxicity, as several studies now report that microplastics negatively affect the central nervous system of fish [19]. Evidence shows that UVSs can affect common biomarkers of neurotoxicity, including acetylcholinesterase activity and neurotransmitter concentrations in fish.

A literature search was conducted on the Web of Science (www.webofknowledge.com) and ScienceDirect (<https://www.sciencedirect.com>) accessed on 1 August 2023 using the keywords [benzotriazole UV stabilizers or benzotriazole UV filters + aquatic environment or water or sludge or sediment]. A total of 365 papers were collected and surveyed for information regarding environmental concentrations in sediment, soil, and water. Figure 2 displays the number of studies corresponding to each keyword. Of these, 64 toxicological studies on the neurotoxicity of benzotriazole UV stabilizers and benzophenone UV filters were identified using the keywords [UVSs + neurotoxicity OR nervous system OR locomotion behavior OR anxiety]. Of these studies, there were 11 reports on neurotoxic endpoints (molecular, biochemical, and behavioral) of UVSs in fish. Data from

these studies were synthesized to generate a more complete understanding of how BUVSs may affect neural-related endpoints and identify potential knowledge gaps in the literature.

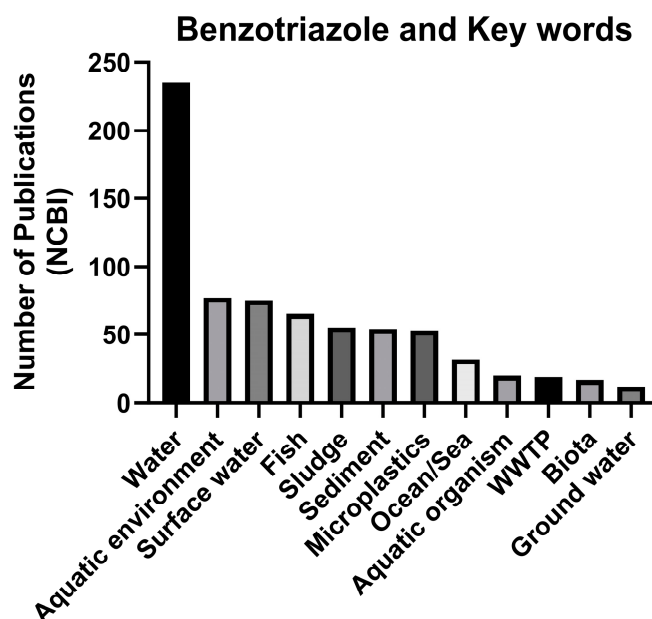


Figure 2. The number of studies corresponding to keywords searched.

3. Occurrence of Ultraviolet Stabilizers in Aquatic Environments

BUVSs can be deposited in aquatic ecosystems via wastewater treatment plant discharges [20], runoff [21], landfills [22], and plastic debris [8,23,24]. These chemicals have been detected in environmental samples such as surface water [14], wastewater [25], seawater [26], sediment [14,27], and sewage sludge [22,28]. Supplemental Table S1 summarizes data for global benzotriazole concentrations. Limited studies examine environmental concentrations in Africa, Australia, and South America, as only four studies in total have reported benzotriazole concentrations at these locations. In North America, multiple studies evaluate concentrations of BUVSs in the USA or Canada; however, most studies available that report on benzotriazole concentrations are in Europe and Asia, in countries such as Spain, China, and India. Briefly, BUVSs (e.g., UV-P, UV-320, UV-326, UV-327, UV-328, and UV-329) were detected in water from rivers in central India at concentrations up to 6.79 ng/L [14], while UV-360 was detected in Gran Canaria seawater at concentrations ranging from 41.12 to 544.9 ng/L [26]. BUVSs (e.g., UV-P, UV-329, UV-326, UV-328, UV-327, UV-571, and UV-360) were present in Gran Canaria (Spain) wastewater at concentrations up to 83.3 ng/L (UV-326) [25]. Additionally, they were detected at concentrations ranging from 0.3 to 320 ng/g dry weight [27] and from 44 to 2362 ng/g dry weight [22] in sediment and sewage sludge, respectively. Studies have also detected BUVSs in human breast milk [29], urine [30], indoor dust [31], and in the tissues of fish, birds, and other aquatic organisms [22,32–34]. Due to their high lipophilicity, BUVSs show a high propensity to bioaccumulate in aquatic organisms [35]. For instance, reports indicate that BUVSs can reach up to 450 ng/g lipid weight in mussels analyzed across 10 countries [34]. Figure 3 provides an overview of BUVS concentration globally.

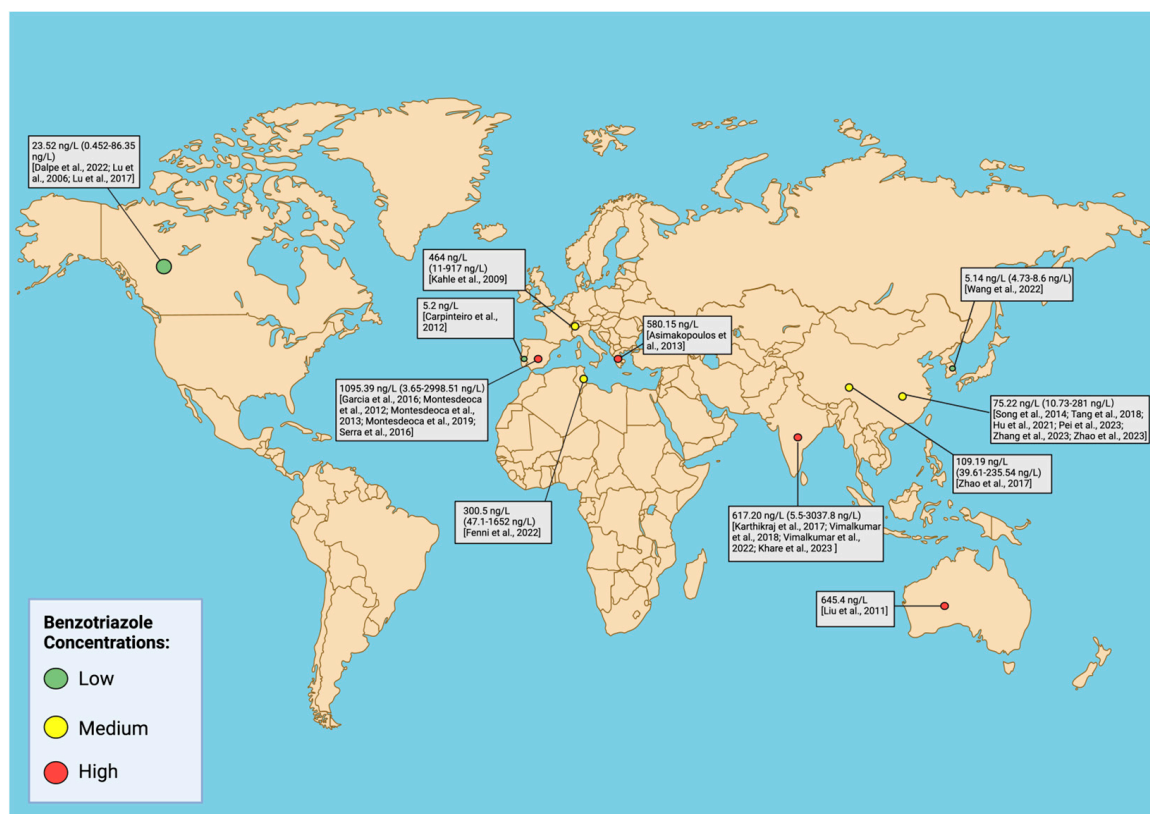


Figure 3. A global map summarizing benzotriazole and benzophenone concentrations in surface water and wastewater. Supplemental Table S2 categorizes concentrations by country/region [14,20,25,26,36–56]. Created with BioRender.com.

4. Neurotoxicity of Ultraviolet Stabilizers in Fish

The health of the central nervous system is critical to all physiological processes in an individual. Unfortunately, there is a plethora of environmental contaminants that can induce neurotoxicity in fish, including pesticides, industrial chemicals, and plastic debris. Researchers have utilized several cellular, biochemical, and molecular endpoints for evaluating the neurotoxicity potential of chemicals, including enzyme activity like acetylcholinesterase or molecular indicators of neuronal or glial damage (e.g., beta-tubulin, microtubule-associated protein tau, glial fibrillary acidic protein). In the following section below, we discuss studies that support or refute the hypothesis that benzotriazoles induce neurotoxicity in fish. Zebrafish were of focus as they share many genes and neurotransmitters, as well as a similar central nervous system structure, with humans, which make them valuable models of neurotoxicity. Table 1 provides a summary of the neurotoxic endpoints assessed and the outcomes of the exposure experiments in fish. However, we also point out that there are additional studies on marine species, mainly bivalves, that address the toxicity of BUVSs. We have included this information in Supplemental Table S3 as a resource to guide future studies in marine invertebrates.

Table 1. Summary of neurotoxic endpoints and outcomes in zebrafish following chemical exposure.

Chemicals	Dose	Life Stage	Exposure Period	Endpoint	Results	Reference
UV-234, UV-326	1, 10, 100 µg/L	Embryos	7d	AchE activity	Upregulated at 10 and 100 µg/L	Zhang et al., 2023 [57]
				Locomotor response	Both compounds induced hyperactivity in the dark cycle via swimming distance, acceleration, and mobile activity.	
				Neurotrophic factors	igf1 and sdf1a were inhibited 1.65- to 2.26-fold and 2.15- to 2.19-fold, respectively, with UV-234; mmp9, fgf2, and sdf1a increased with 1 and 100 µg/L UV-326; igf1 decreased with 10 µg/L exposure UV-326	
				Spontaneous tail coiling (STC)	Inhibited 2.08–6.25-fold	
				Pro-inflammatory gene expression	<i>tnfa</i> decreased in all treatment. <i>il1β</i> decreased with 100 µg/L UV-234 and increased with 100 µg/L UV-326; <i>il6</i> increased with 100 µg/L UV-326	
UV-234, UV-320	0.01, 0.1, 1 µM	Embryos	6d	Locomotor response	UV-234 altered activity in both light/dark periods; Hyperactivity was induced in fish pre-adapted to darkness with 1 µM UV-320; 1 µM UV-320 increased distance moved in the dark phase; 0.1 µM UV-320 increased distance moved in the light phase	Liang et al., 2019 [58]
BP3	1, 10, 100 µg/L	Embryos and larvae	4d	Axonal Growth	Decreased relative axon length in 27 hpf larvae.	Tao et al., 2020 [59]
				Touch response	Decreased in 27 hpf larvae with 10 µg/L	
				Locomotor response	Increased swimming distance and average swimming speed in the dark period with 10 µg/L	
				Spontaneous movement	Increased frequency of bending at 21 hpf (10 and 100 µg/L) and 24 hpf (10 µg/L)	
				Social behaviors	Nearest neighbor distance and the inter-individual distance increased; Mean attacks and time spent in the mirror area decreased	
BP3	10 µg/L	Adults	150d	Social preference	Reduced prosocial behaviors	Bai et al., 2023 [60]
				Mirror biting test	Reduction of biting behavior in females	
				T-maze test	Impaired learning and memory regardless of sex	
				Body length, weight, brain weight, brain dopamine and acetylcholine	Reduced female brain weight and dopamine level	
				Cell proliferation in the telencephalon	Neurogenesis inhibited in the telencephalon	
				Cell apoptosis in the telencephalon	Apoptotic cells increased in the female telencephalon	

Table 1. Cont.

Chemicals	Dose	Life Stage	Exposure Period	Endpoint	Results	Reference
BP3	2 mg/L	Larvae	5d	Enteric neuron number and related gene expression	BP-3 could impede ENS zebrafish development via the MAPK/ERK signaling pathway	Hemalatha et al., 2020 [61]
BP3	1, 10 µg/L	Embryos	3d	AChE	Inhibited by both concentrations	Sandoval-Gío et al., 2021 [62]
BP3	10, 100, 1000 µg/L	Adults	15d	Novel tank test Shoal preference Mirror test T-maze	Reduced locomotion and decreased anxiety-like behavior Reduced interaction and time near the shoal Reduced interactions with the mirror image; thus, impairing proper aggressive response Reduced exploration of the novel arm; thus, jeopardizing the ability to retain information	Moreira et al., 2022 [63]
BP3, nano-Tio2	10 µg/L BP3; 100 µg/L nano-Tio2 (separately and combined)	Embryos	1d	Spontaneous movement Touch response Axonal growth	Increased in single and coexposure groups at 24 hpf Decreased in co-exposure at 30 hpf Single and coexposure inhibited axonal growth, and induced apoptosis and ROS generation	Sun et al., 2023 [64]
BP1	0.8, 1, 1.2, 1.6, 2.4 µg/mL	Larvae	4d 6d	CNS DA neurons Locomotor capacity	Abnormal brain structure and neuron loss Decreased the number in the midbrain Suppressed velocity and movement distance; altered expression of neurodevelopment related genes	Song et al., 2022 [65]
BP1	1, 10, 100, 1000 µg/L	Adults	14d	T-maze tests Tank diving tests	Inhibited spatial working memory Increase in proportion of bottom swimming duration/distance to total duration/distance, indicating a decrease of exploratory behavior	

4.1. Molecular and Biochemical Indicators of Neurotoxicity

There have been several studies reporting the neurotoxic effects of BUVSs at the cellular and molecular level. Song et al. [65] exposed larval zebrafish (*Danio rerio*) to 0.8, 1, 1.2, 1.6, or 2.4 µg/mL and adult zebrafish to 1, 10, 100, or 1000 µg/L benzophenone-1 (BP-1) and reported that BP-1 decreased the number of dopaminergic neurons in the midbrain and induced the loss of neurons in the central nervous system (midbrain and thalamus) in a concentration-dependent manner. Zebrafish exposed to 2.4 µg/mL also lost a significant number of neurons in their tails. Neurodevelopment-related genes in larvae were also measured in the study following 6 days of exposure. Following exposure to 1.6 and 2.4 µg/mL, brain-derived neurotrophic factor (*bdnf*) and myelin basic protein a (*mbpa*) decreased and increased in expression, respectively. Additionally, pro-opiomelanocortin (*pomc*) expression

was reduced in fish exposed to 0.8 and 1.0 µg/mL, and glial fibrillary acidic protein (*gfap*) expression was reduced in fish exposed to between 1.0 and 2.4 µg/mL [65]. Additional studies support the hypothesis that BUVs induce oxidative stress and neuroinflammation in fish. For example, Sun et al. [64] exposed zebrafish embryos to 10 or 100 µg/L benzophenone-3 (BP-3) or titanium dioxide nanoparticles (nano-TiO₂) for 1 day, either separately or in a mixture. Single and co-exposure to BP-3 induced apoptosis, inhibited axonal growth, and generated reactive oxygen species (ROS). The immune system also appears to be a target for toxicity, indicating the potential for neuroinflammation. In another study, Zhang et al. [57] exposed zebrafish embryos to two common benzotriazole UV stabilizers, UV-234 and UV-326, at concentrations of 1, 10, and 100 µg/L for 7 days. In the study, pro-inflammatory gene expression was analyzed, and it was found that the two stabilizers had varying effects on the organism, suggesting differences in mechanisms of toxicity. In fish exposed to 100 µg/L UV-326, interleukin-1 beta (*il1β*) and interleukin 6 (*il6*) were significantly increased; however, *il1β* was significantly decreased in fish exposed to 100 µg/L UV-234. Tumor necrosis factor α (*tnfα*), a pro-inflammatory cytokine, was significantly decreased following both stabilizer treatments. Insulin-like growth factor 1 (*igf1*) and stromal cell-derived factor 1 (*sdf1a*) were inhibited 1.65- to 2.26-fold and 2.15- to 2.19-fold, respectively, following UV-234 exposure, which indicates damage to cell differentiation and regeneration function. In fish exposed to UV-326, *igf1* decreased with 10 µg/L, but fibroblast growth factor 2 (*fgf2*), matrix metalloproteinase 9 (*mmp9*), and *sdf1a* increased with exposure to 1 or 100 µg/L UV-326, indicating the initiation of nerve cell repair following an inflammatory reaction [57]. Furthermore, at the biochemical level, exposure to BP-3 for 3 days decreased acetylcholinesterase (AChE) activity and increased AChE gene expression in a concentration-dependent manner in zebrafish [62]. Taken together, oxidative stress, neuroinflammation, and effects on AChE are notable mechanisms of toxicity for BUVs.

4.2. Behavioral Indicators of Neurotoxicity

Behavioral assays have been utilized to identify interactions of ultraviolet stabilizers with the nervous system. Behavioral endpoints measured that provide sensitive indicators for neuroactivity of BUVs in fish have included spontaneous tail coiling (STC), alternating light- and dark-induced locomotor response (LMR-L/D), and social behaviors such as shoaling, and mirror response (Table 1). To date, several toxicological studies have reported on ultraviolet filters, including benzophenone derivatives like BP-1 and BP-3 (BP-3 being the most studied) [66]. These studies have been conducted on both larval and adult fish. Tao and colleagues [59] exposed zebrafish embryos to 1, 10, or 100 µg/L BP-3 for up to 4 days. Axon length was decreased in 27 hpf larvae, and cell apoptosis in the head region increased in all treated embryos. Concerning motor and social behavior analysis, only embryos exposed to 10 µg/L were analyzed. Response rates in 27 hpf larvae were reduced, but this effect was not observed in 48 hpf larvae. Swimming distance and speed were increased at 5 dpf, the nearest neighbor distance and the inter-individual distance increased significantly at 11 dpf, and the mean number of times fish butted/bit or spent around the mirror during the mirror response test were significantly decreased at 12 dpf. In another study, larval zebrafish exposed to between 0.8 and 2.4 µg/mL BP-1 for 6 days showed reduced velocity when exposed to the highest tested concentration [59]. Sun et al. [64] exposed zebrafish embryos separately or in a mixture to 10 or 100 µg/L BP-3 or nano-TiO₂ for 1 day. At 24 hpf, both single and co-exposure significantly increased spontaneous movement, and, at 30 hpf, co-exposure of the chemicals caused the touch response rate to decrease.

Adult fish behavioral responses have also been investigated following BUVs exposure. Moreira and Luchiari [57] analyzed the response of adult zebrafish exposed to 10, 100, or 1000 µg/L BP-3 following several administered tests (i.e., T-maze, shoal preference, mirror test, novel tank test). Decreased exploration and interaction of the novel arm in the T-maze and with the shoal preference test were observed in fish, along with fewer mirror image interactions, decreased anxiety-like behavior, and decreased locomotion. Furthermore, Bai

et al. [60] exposed adult zebrafish to 10 µg/L BP-3 for 150 days and analyzed behavioral alterations and cognitive deficits. Following a social preference test, fish were observed to have reduced prosocial behaviors. Additionally, biting behavior in females was significantly reduced. Both male and female fish were found to display impaired learning and memory and neurogenesis inhibition [60]. In female fish, brain weight and dopamine levels were reduced, and the number of apoptotic cells in their telencephalon was increased. In another study using a T-maze test in adult zebrafish exposed to BP-1, impaired learning and memory ability were observed as retention time decreased and latency to deep water increased in a concentration-dependent manner [25]. The total swimming distance in adults also decreased in a concentration-dependent manner, and the swimming duration at the bottom of the tank increased, indicating that BP-1 decreases exploratory behavior at the top of the tank (i.e., increases anxiety).

Conversely, behavioral studies on UV stabilizers are limited. As a derivative of the suspected neurotoxin benzotriazole [67], many BUVS congeners are reported to disrupt swimming behavior in early-stage zebrafish. Liang et al. [58] exposed zebrafish embryos to 0.01, 0.1, or 1.0 µM UV-234 or UV-320 for 6 days and conducted a light/dark locomotor response assay. There were subtle behavioral responses that were chemically dependent. Concerning fish in the UV-234 exposure group, larvae pre-adapted to darkness and exhibited decreased locomotor activity during the beginning of the assay. Zebrafish larvae exposed to 0.1 and 1 µM exhibited a decrease in overall distance moved, whereas fish exposed to 0.01 µM exhibited an increase in distance moved. Concerning fish in the UV-320 exposure group, larvae pre-adapted to darkness at the beginning of the assay and exhibited decreased activity. Fish pre-adapted to darkness and exposed to 1 µM initially exhibited increased activity and distance moved but exhibited a decrease in distance moved near the end of the exposure. Additionally, fish treated with 0.1 µM exhibited increased distance moved during the light phase of the assay. Thus, it appears that the type of BUVS and its concentration can induce variable responses in zebrafish larvae. In another study, Zhang et al. [57] exposed zebrafish embryos to UV-234 and UV-326 at 1, 10, and 100 µg/L for 7 days. Concerning behavioral alterations following a light/dark locomotor response assay, both compounds were found to induce hyperactivity during the dark cycles of the assay, where acceleration, mobile activity, and swimming distance were increased. Additionally, spontaneous tail coiling was inhibited 2.08–6.25-fold from 28–29 hpf following exposure to both stabilizers. Noteworthy is that these behavioral responses corresponded to the activity of AChE, which was elevated in fish exposed to 10 and 100 µg/L UV-234 and UV-326. Taken together, aberrant behavior has been associated with BUVS-induced apoptosis and ROS generation, which subsequently influence neuroinflammation and cell regeneration processes [57]. Similar molecular events have also been observed in Asian clams (*Corbicula fluminea*) [68], where impairment of the oxidative defense system induced by BUVSs triggered an increase in the neurotransmitter acetylcholine, causing accelerated filtration and tissue damage, suggesting that the neurotoxic effects of BUVSs may not be limited to aquatic vertebrates.

5. Biomarkers of Toxicity: Neurotoxic Indicators?

To uncover molecular responses underlying benzotriazole and benzotriazole derivatives, we extracted molecular interactions for further investigation using Pathway Studio (V12) as per our previous methods [69,70]. Genes differentially affected by benzotriazole were extracted from the comparative toxicogenomics database (CTD) [71]. We were able to identify cell processes, cell components, clinical parameters, proteins, and other functional classes with direct connections to benzotriazole. These interactions have been implicated in experiments investigating benzotriazoles.

There were over 50 entities that were associated with benzotriazole exposure. Several small molecules were linked to benzotriazoles (i.e., ozone, chloroform, Cd²⁺, and chlorine), as well as several viral entities (i.e., hepatitis C, HIV-1) and pathogens (i.e., *Candida albicans* and *Mycobacterium tuberculosis*) (Figure 4). Other notable entities associated with

benzotriazoles included chemotaxis, oxidative stress, DNA recombination, mitochondrial, genotoxicity, endometrial carcinoma, and liver atrophy. Transcripts or proteins responsive to benzotriazoles included PTPN1 (protein tyrosine phosphatase non-receptor type 1), PTGES (prostaglandin E synthase), GNRH1 (gonadotropin releasing hormone 1), AHR (aryl hydrocarbon receptor), CDH1 (cadherin 1), and CDK2 (cyclin dependent kinase 2). Many of these proteins have been implemented in neurodegenerative diseases and are linked to protective effects for neural toxicity. For example, paraoxonase-1 can neutralize environmental toxicants to protect lipids against peroxidation. Consequently, the deterioration and absence of paraoxonase-1 removes mechanisms responsible for breaking down neurotoxic compounds, which can increase a species' vulnerability to neurotoxic consequences [72,73]. CDH1 is a transmembrane protein involved in mediating cell-to-cell adhesion, thus playing a significant role in tissue homeostasis, including in the blood-brain barrier. Transcription of cadherin-1 has been found to increase in the presence of neuronal degeneration and astrocyte swelling following silver nanoparticle exposure, which demonstrates its protective effects against neurotoxicity [74]. CDK2 positively regulates cell cycle progression and has been found to be essential in mice for the regeneration and growth of neural progenitor cells [75]. Disruption to the regeneration and proliferation of progenitor cells can alter the communication abilities of the central nervous system. Lastly, AHR connects environmental chemical inputs to adaptive reactions, including metabolic processes and immunological responses. Disruption of the receptor, specifically its inactivation, has been found to negatively regulate transcriptional responses related to microglial activation and neurotoxic monocyte recruitment [76].

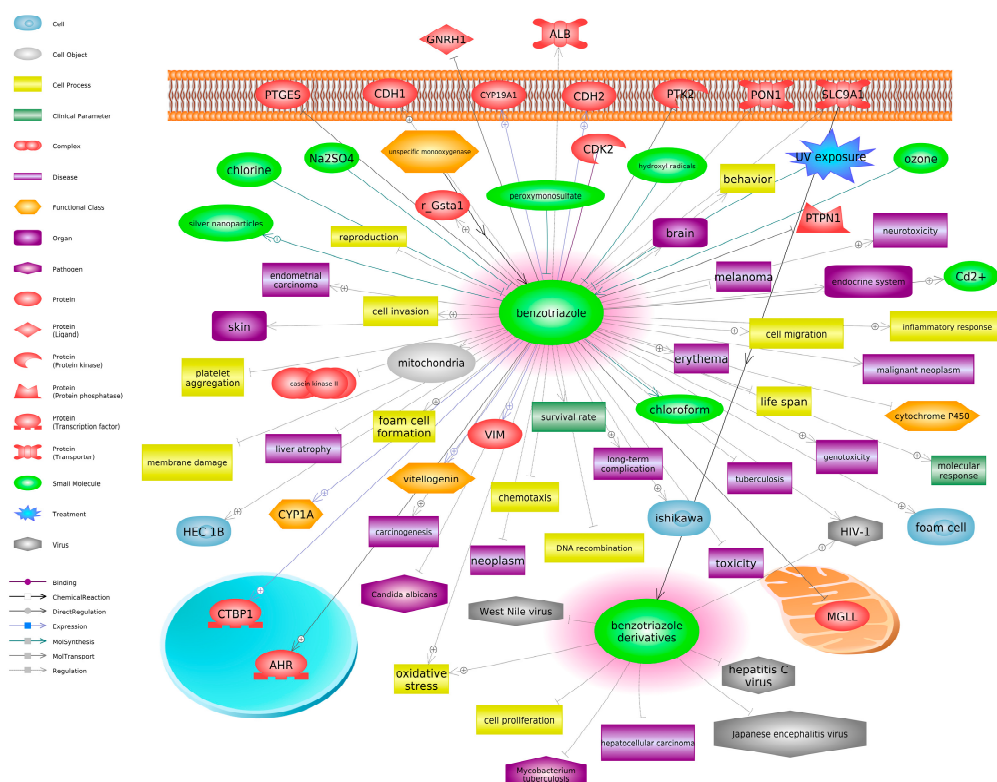


Figure 4. Functional classes and proteins associated with benzotriazole [Pathway Studio (Elsevier)]. Abbreviations for the figure are presented in Supplemental Data S1.

In addition, gene set enrichment revealed pathways like “Complement Activation in Alzheimer’s Disease”, “MPB-Related Complement Cascade Activation”, and “Positive Acute Phase Protein Synthesis” were associated with BUVs exposure (Table 2). Some studies report upregulated AChE activity following UV-234 and UV-326 exposure [57], which

can result in increased amyloid-beta deposition, thus contributing to Alzheimer's disease. Such targets can be further investigated for their role in BUVS-induced neurotoxicity.

Table 2. Gene set enrichment of genes regulated by benzotriazole ($p < 0.001$). The name of the pathway, the number (#) of entities in the pathway, and the overlap between regulated genes and those in the pathway. percent overlap, p -value, and hit type are included in the table.

Name	Expanded # of Entities	Overlap	Percent Overlap	Hit Type
Complement Activation in Alzheimer's Disease	36	10	27	Disease
MPB-Related Complement Cascade Activation	39	10	25	Disease
Positive Acute Phase Proteins Synthesis	609	20	3	Biological Process
Trophoblast Damage in Infertility (Hypothesis)	61	10	16	Disease
CD46/CD55/CD59 Inhibit Complement Mediated Lysis of Cancer Cells	50	10	20	Pathological Process
Complement Activation in Glomerulonephritis	63	10	15	Disease
Complement System Defects in Systemic Lupus Erythematosus	73	10	13	Disease
Complement Activation by Lectin	68	10	14	Biological Process
Extraocular Muscles Weakness in Myasthenia Gravis	84	10	11	Disease
Complement Classical Pathway	71	10	14	Biological Process

Evidence for neurotoxicity was also noted in the interaction network with cell invasion, membrane damage, and behavior (Figure 4); thus, evidence suggests the neural and immune systems are relevant targets for adverse outcomes related to benzotriazole exposure. Such relationships have yet to be investigated in fish, presenting an opportunity to investigate novel mechanisms of action for this chemical class. Pathways responsive to BUVSs retrieved from the Comparative Toxicogenomics Database [71] included glutathione conjugation, glutathione metabolism, drug metabolism, cytochrome P450, and regulation of Toll-like receptors (TLRs) by endogenous ligands. Benzotriazoles have been shown to affect these processes in animals. He et al. [77] exposed marine medaka (*Oryzias melastigma*) to 0.01–1.0 mg/L benzotriazole for 35 days and observed decreased expression of cytochrome P450 1A1 (*cyp1A1*) in the liver and intestines of fish, which is responsible for steroidal hormone metabolism and immune response enhancement. Another study conducted by Hemalatha et al. [61] found that BUV-328 elevated glutathione S-transferase in adult zebrafish exposed to 0.01–1 mg/L for up to 42 days, denoting the metabolism of lipid peroxides and the biotransformation of toxic compounds. Additionally, zebrafish embryos exposed to 15.8–690 µg/L 2-(2-Hydroxy-5-methylphenyl) benzotriazole (UV-P) exhibited a dose-related induction of glutathione-S-transferase, whereas the opposite effect was observed in fish exposed to 7.5–84.3 µg/L UV-326 for 6 days [78]; these data suggest that benzotriazole and its derivatives have varying impacts on detoxification processes, which is accomplished by the catalytic conjugation of glutathione. The computational analysis also points to glutathione depletion, oxidative stress, and neuro-inflammation as underlying neurological dysfunction and behavioral abnormalities following BUVS exposure.

6. Conclusions

Studies report low acute toxicity of BUVSs to fish; however, the ecotoxicological risk to species is not fully elucidated. Benzotriazoles and their derivatives are highly stable in soil/water due to their physiochemical properties, which allow them to persist in the environment. In soil, benzotriazole has been reported to have a half-life of 180 days at 20 °C, and, in freshwater, its half-life is 831 days at 12 °C (<https://echa.europa.eu/registration-dossier/-/registered-dossier/14234/5/3/4>) (accessed on 1 August 2023). Though most studies report benzotriazoles and their derivatives in ng/L, with the compound's resistance to biodegradation and its continued utilization, it can accumulate in the environment, thus posing threats to aquatic organisms. We point out deficiencies in the literature currently related to the neurotoxicity of BUVSs. These knowledge gaps include the following:

- (1) In-depth mechanistic studies on the central nervous system of zebrafish are needed to address neurotoxicity. Validation of specific neurotoxicity pathways relevant for BUVS exposure is needed.
- (2) Broader scope of behavioral assays related to the dopaminergic systems, such as anxiety-related and fear-related behaviors, given that the exploration of novel tank environments by fish is altered with exposures.
- (3) Histopathology of the central nervous system is needed following exposure to these chemicals, given evidence for neuronal damage, apoptosis, and neurodegeneration.
- (4) Ecologically important species would broaden the scope and environmental relevance of laboratory-based studies, as most studies are conducted using zebrafish. Nevertheless, the zebrafish model has proven useful for developmental toxicity studies for plasticizers and has improved our understanding of toxicity mechanisms in fish.
- (5) Based on our review, several studies report neurological responses above environmental levels (Figure 5), although there are experimental data that correspond to environmental levels.

Biological Effects of Benzotriazole vs Environmental Levels

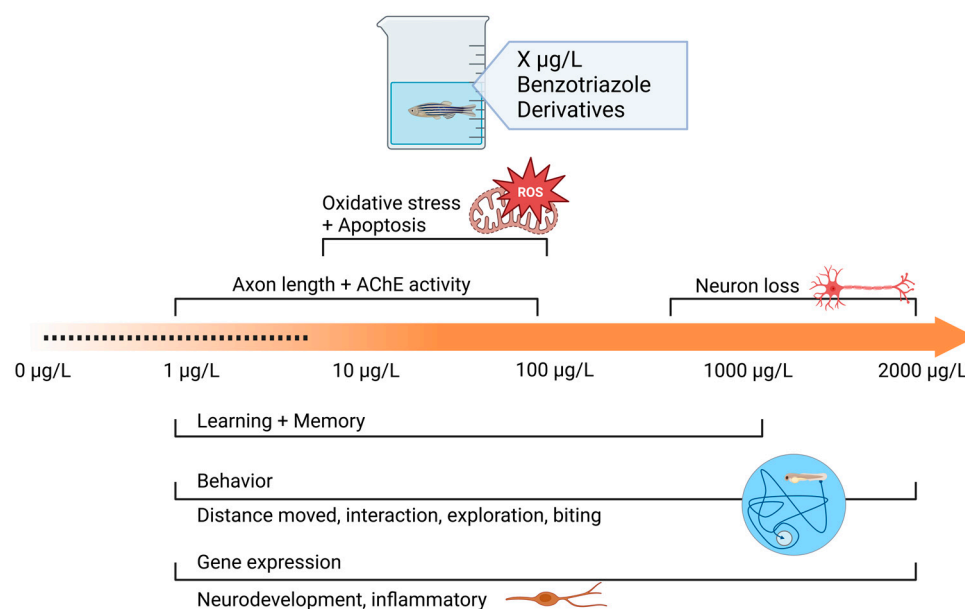


Figure 5. The neurotoxic effects of benzotriazole in fish compared to measured environmental concentrations (dashed line indicates environmental levels). Created with BioRender.com.

One final point to make is that most concentration data are collected in non-marine environments. Benzotriazoles and benzophenone can also exert toxic effects on marine organisms like sea urchin larvae and coral [79,80]. However, to our knowledge, the studies on adverse effects on marine fish are limited. Research efforts in these areas are expected to

fill knowledge gaps regarding the effects of UV stabilizers in the central nervous system of fish and aquatic species in general. Such approaches will facilitate risk assessments and identify safe environmental levels for this ubiquitous class of chemicals.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/toxics12020125/s1>, Supplemental Table S1: Occurrence of ultraviolet stabilizers in aquatic environments. Supplemental Table S2: Occurrence of ultraviolet stabilizers in aquatic environments. Supplemental Table S3: presents data for marine invertebrates. Supplemental Data S1: contains all abbreviations for the pathway in Figure 4. References [81–98] are cited in the supplementary materials.

Author Contributions: Conceptualization, X.L. and C.J.M.; methodology, M.L., E.I. and X.L.; formal analysis, M.L., E.I. and X.L.; writing—original draft preparation, M.L., E.I., X.L. and C.J.M.; writing—review and editing, M.L., E.I., X.L. and C.J.M.; supervision, X.L. and C.J.M.; project administration, X.L. and C.J.M.; funding acquisition, C.J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the University of Florida and the College of Veterinary Medicine (CJM).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original data presented in the study are included in the article/Supplementary Materials.

Conflicts of Interest: The authors declare no conflicts of interest.

References

- Do, A.T.N.; Ha, Y.; Kwon, J.H. Leaching of microplastic-associated additives in aquatic environments: A critical review. *Environ. Pollut.* **2022**, *305*, 119258. [CrossRef]
- Rahman, M.; Brazel, C.S. The plasticizer market: An assessment of traditional plasticizers and research trends to meet new challenges. *Prog. Polym. Sci.* **2004**, *29*, 1223–1248. [CrossRef]
- Bernard, L.; Bourdeaux, D.; Pereira, B.; Azaroual, N.; Barthelemy, C.; Breyse, C.; Chennell, P.; Cuffe, R.; Dine, T.; Eljezi, T.; et al. Analysis of plasticizers in PVC medical devices: Performance comparison of eight analytical methods. *Talanta* **2017**, *162*, 604–611. [CrossRef]
- Billings, A.; Jones, K.C.; Pereira, M.G.; Spurgeon, D.J. Plasticisers in the terrestrial environment: Sources, occurrence and fate. *Environ. Chem.* **2021**, *18*, 111–130. [CrossRef]
- Jia, P.Y.; Xia, H.Y.; Tang, K.H.; Zhou, Y.H. Plasticizers Derived from Biomass Resources: A Short Review. *Polymers* **2018**, *10*, 1303. [CrossRef]
- Wormuth, M.; Scheringer, M.; Vollenweider, M.; Hungerbühler, K. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? *Risk Anal.* **2006**, *26*, 803–824. [CrossRef] [PubMed]
- Hahladakis, J.N.; Velis, C.A.; Weber, R.; Iacovidou, E.; Purnell, P. An overview of chemical additives present in plastics: Migration, release, fate and environmental impact during their use, disposal and recycling. *J. Hazard. Mater.* **2018**, *344*, 179–199. [CrossRef] [PubMed]
- Rani, M.; Shim, W.J.; Han, G.M.; Jang, M.; Song, Y.K.; Hong, S.H. Benzotriazole-type ultraviolet stabilizers and antioxidants in plastic marine debris and their new products. *Sci. Total Environ.* **2017**, *579*, 745–754. [CrossRef] [PubMed]
- Kim, J.-W.; Isobe, T.; Ramaswamy, B.R.; Chang, K.-H.; Amano, A.; Miller, T.M.; Siringan, F.P.; Tanabe, S. Contamination and bioaccumulation of benzotriazole ultraviolet stabilizers in fish from Manila Bay, the Philippines using an ultra-fast liquid chromatography-tandem mass spectrometry. *Chemosphere* **2011**, *85*, 751–758. [CrossRef] [PubMed]
- Montesdeoca-Esponda, S.; Vega-Morales, T.; Sosa-Ferrera, Z.; Santana-Rodriguez, J.J. Extraction and determination methodologies for benzotriazole UV stabilizers in personal-care products in environmental and biological samples. *Trac.-Trends Anal. Chem.* **2013**, *51*, 23–32. [CrossRef]
- Chisvert, A.; Leon-Gonzalez, Z.; Tarazona, I.; Salvador, A.; Giokas, D. An overview of the analytical methods for the determination of organic ultraviolet filters in biological fluids and tissues. *Anal. Chim. Acta* **2012**, *752*, 11–29. [CrossRef]
- Sanchez-Quiles, D.; Tovar-Sanchez, A. Are sunscreens a new environmental risk associated with coastal tourism? *Environ. Int.* **2015**, *83*, 158–170. [CrossRef] [PubMed]
- Sakuragi, Y.; Takada, H.; Sato, H.; Kubota, A.; Terasaki, M.; Takeuchi, S.; Ikeda-Araki, A.; Watanabe, Y.; Kitamura, S.; Kojima, H. An analytical survey of benzotriazole UV stabilizers in plastic products and their endocrine-disrupting potential via human estrogen and androgen receptors. *Sci. Total Environ.* **2021**, *800*, 149374. [CrossRef] [PubMed]

14. Khare, A.; Jadhao, P.; Kawre, S.; Kanade, G.; Patil, M.; Vaidya, A.N.; Kumar, A.R. Occurrence, spatio-temporal variation and ecological risk assessment of benzotriazole ultraviolet stabilizers (BUVs) in water and sediment of rivers in central India. *Sci. Total Environ.* **2023**, *882*, 163381. [\[CrossRef\]](#) [\[PubMed\]](#)
15. OECD. HPV Database. Available online: <https://hpvchemicals.oecd.org/UI/Search.aspx> (accessed on 31 October 2023).
16. Fujita, K.K.; Doering, J.A.; Stock, E.; Lu, Z.; Montina, T.; Wiseman, S. Effects of dietary 2-(2H-benzotriazol-2-yl)-4-methylphenol (UV-P) exposure on Japanese medaka (*Oryzias latipes*) in a short-term reproduction assay. *Aquat. Toxicol.* **2022**, *248*, 106206. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Li, Z.; Liang, X.; Liu, W.; Zhao, Y.; Yang, H.; Li, W.; Adamovsky, O.; Martyniuk, C.J. Elucidating mechanisms of immunotoxicity by benzotriazole ultraviolet stabilizers in zebrafish (*Danio rerio*): Implication of the AHR-IL17/IL22 immune pathway. *Environ. Pollut.* **2020**, *262*, 114291. [\[CrossRef\]](#)
18. Kim, H.; Kim, B.; Shin, Y.-J.; Kim, J.; Kim, H.-j.; Kim, K.; Kim, P.; Park, K. Effect of benzotriazole on oxidative stress response and transcriptional gene expression in *Oryzias latipes* and *Danio rerio* embryo. *Comp. Biochem. Physiol. Part C Toxicol. Pharmacol.* **2022**, *252*, 109222. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Barboza, L.G.A.; Otero, X.L.; Fernández, E.V.; Vieira, L.R.; Fernandes, J.O.; Cunha, S.C.; Guilhermino, L. Are microplastics contributing to pollution-induced neurotoxicity? A pilot study with wild fish in a real scenario. *Heliyon* **2023**, *9*, e13070. [\[CrossRef\]](#)
20. Lu, Z.; Smyth, S.A.; Peart, T.E.; De Silva, A.O. Occurrence and fate of substituted diphenylamine antioxidants and benzotriazole UV stabilizers in various Canadian wastewater treatment processes. *Water Res.* **2017**, *124*, 158–166. [\[CrossRef\]](#)
21. Awonaike, B.; Lei, Y.D.; Parajulee, A.; Wania, F. Phase partitioning, transport and sources of Benzotriazole Ultraviolet Stabilizers during a runoff event. *Water Res. X* **2021**, *13*, 100115. [\[CrossRef\]](#)
22. Langford, K.H.; Reid, M.J.; Fjeld, E.; Øxnevad, S.; Thomas, K.V. Environmental occurrence and risk of organic UV filters and stabilizers in multiple matrices in Norway. *Environ. Int.* **2015**, *80*, 1–7. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Fukuoka, T.; Sakane, F.; Kinoshita, C.; Sato, K.; Mizukawa, K.; Takada, H. COVID-19-derived plastic debris contaminating marine ecosystem: Alert from a sea turtle. *Mar. Pollut. Bull.* **2022**, *175*, 113389. [\[CrossRef\]](#)
24. Ngoc Do, A.T.; Ha, Y.; Kang, H.J.; Kim, J.M.; Kwon, J.H. Equilibrium leaching of selected ultraviolet stabilizers from plastic products. *J. Hazard. Mater.* **2022**, *427*, 128144. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Montesdeoca-Esponda, S.; del Toro-Moreno, A.; Sosa-Ferrera, Z.; Juan Santana-Rodriguez, J. Development of a sensitive determination method for benzotriazole UV stabilizers in environmental water samples with stir bar sorption extraction and liquid desorption prior to ultra-high performance liquid chromatography with tandem mass spectrometry. *J. Sep. Sci.* **2013**, *36*, 2168–2175. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Garcia-Guerra, R.B.; Montesdeoca-Esponda, S.; Sosa-Ferrera, Z.; Kabir, A.; Furton, K.G.; Juan Santana-Rodriguez, J. Rapid monitoring of residual UV-stabilizers in seawater samples from beaches using fabric phase sorptive extraction and UHPLC-MS/MS. *Chemosphere* **2016**, *164*, 201–207. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Nakata, H.; Murata, S.; Filatreau, J. Occurrence and concentrations of benzotriazole UV stabilizers in marine organisms and sediments from the Ariake Sea, Japan. *Environ. Sci. Technol.* **2009**, *43*, 6920–6926. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Ruan, T.; Liu, R.; Fu, Q.; Thanh, W.; Wang, Y.; Song, S.; Wang, P.; Teng, M.; Jiang, G. Concentrations and Composition Profiles of Benzotriazole UV Stabilizers in Municipal Sewage Sludge in China. *Environ. Sci. Technol.* **2012**, *46*, 2071–2079. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Kim, J.W.; Chang, K.H.; Prudente, M.; Viet, P.H.; Takahashi, S.; Tanabe, S.; Kunisue, T.; Isobe, T. Occurrence of benzotriazole ultraviolet stabilizers (BUVs) in human breast milk from three Asian countries. *Sci. Total Environ.* **2019**, *655*, 1081–1088. [\[CrossRef\]](#)
30. Denghel, H.; Goen, T. Determination of the UV absorber 2-(2H-benzotriazol-2-yl)-4,6-di-tert-pentylphenol (UV 328) and its oxidative metabolites in human urine by dispersive liquid-liquid microextraction and GC-MS/MS. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2020**, *1144*, 122071. [\[CrossRef\]](#)
31. Kim, J.W.; Isobe, T.; Malarvannan, G.; Sudaryanto, A.; Chang, K.H.; Prudente, M.; Tanabe, S. Contamination of benzotriazole ultraviolet stabilizers in house dust from the Philippines: Implications on human exposure. *Sci. Total Environ.* **2012**, *424*, 174–181. [\[CrossRef\]](#)
32. Lu, Z.; De Silva, A.O.; Zhou, W.; Tetreault, G.R.; de Solla, S.R.; Fair, P.A.; Houde, M.; Bossart, G.; Muir, D.C.G. Substituted diphenylamine antioxidants and benzotriazole UV stabilizers in blood plasma of fish, turtles, birds and dolphins from North America. *Sci. Total Environ.* **2019**, *647*, 182–190. [\[CrossRef\]](#)
33. Montesdeoca-Esponda, S.; Esther Torres-Padron, M.; Novak, M.; Krchova, L.; Sosa-Ferrera, Z.; Juan Santana-Rodriguez, J. Occurrence of benzotriazole UV stabilizers in coastal fishes. *J. Environ. Manag.* **2020**, *269*, 110805. [\[CrossRef\]](#)
34. Nakata, H.; Shinohara, R.-I.; Nakazawa, Y.; Isobe, T.; Sudaryanto, A.; Subramanian, A.; Tanabe, S.; Zakaria, M.P.; Zheng, G.J.; Lam, P.K.S.; et al. Asia-Pacific mussel watch for emerging pollutants: Distribution of synthetic musks and benzotriazole UV stabilizers in Asian and US coastal waters. *Mar. Pollut. Bull.* **2012**, *64*, 2211–2218. [\[CrossRef\]](#)
35. Wick, A.; Jacobs, B.; Kunkel, U.; Heininger, P.; Ternes, T.A. Benzotriazole UV stabilizers in sediments, suspended particulate matter and fish of German rivers: New insights into occurrence, time trends and persistency. *Environ. Pollut.* **2016**, *212*, 401–412. [\[CrossRef\]](#)
36. Asimakopoulou, A.; Alexandros, G.; Ajibola, A.; Kannan, K.; Thomaidis, N.S. Occurrence and removal efficiencies of benzotriazoles and benzothiazoles in a wastewater treatment plant in Greece. *Sci. Total Environ.* **2013**, *452*, 163–171.

37. Carpinteiro, I.; Ramil, M.; Rodriguez, I.; Nogueira, J.M.F. Combining stir-bar sorptive extraction and large volume injection-gas chromatography-mass spectrometry for the determination of benzotriazole UV stabilizers in wastewater matrices. *J. Sep. Sci.* **2012**, *35*, 459–467. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Castilloux, A.D.; Houde, M.; Gendron, A.; De Silva, A.; Soubaneh, Y.D.; Lu, Z. Distribution and Fate of Ultraviolet Absorbents and Industrial Antioxidants in the St. Lawrence River, Quebec, Canada. *Environ. Sci. Technol.* **2022**, *56*, 5009–5019. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Fenni, F.; Sunyer-Caldu, A.; Mansour, H.B.; Diaz-Cruz, M.S. Contaminants of emerging concern in marine areas: First evidence of UV filters and paraben preservatives in seawater and sediment on the eastern coast of Tunisia. *Environ. Pollut.* **2022**, *309*, 119749. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Hu, L.X.; Cheng, Y.X.; Wu, D.; Fan, L.; Zhao, J.H.; Xiong, Q.; Chen, Q.L.; Liu, Y.S.; Ying, G.G. Continuous input of organic ultraviolet filters and benzothiazoles threatens the surface water and sediment of two major rivers in the Pearl River Basin. *Sci. Total Environ.* **2021**, *798*, 149299. [\[CrossRef\]](#) [\[PubMed\]](#)
41. Kahle, M.; Buerge, I.J.; Muller, M.D.; Poiger, T. Hydrophilic anthropogenic markers for quantification of wastewater contamination in ground- and surface waters. *Environ. Toxicol. Chem.* **2009**, *28*, 2528–2536. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Karthikraj, R.; Kannan, K. Mass loading and removal of benzotriazoles, benzothiazoles, benzophenones, and bisphenols in Indian sewage treatment plants. *Chemosphere* **2017**, *181*, 216–223. [\[CrossRef\]](#)
43. Liu, Y.-S.; Ying, G.-G.; Shareef, A.; Kookana, R.S. Simultaneous determination of benzotriazoles and ultraviolet filters in ground water, effluent and biosolid samples using gas chromatography-tandem mass spectrometry. *J. Chromatogr. A* **2011**, *1218*, 5328–5335. [\[CrossRef\]](#)
44. Lu, J.; Li, H.; Luo, Z.; Lin, H.; Yang, Z. Occurrence, distribution, and environmental risk of four categories of personal care products in the Xiangjiang River, China. *Environ. Sci. Pollut. Res.* **2018**, *25*, 27524–27534. [\[CrossRef\]](#)
45. Lu, Z.; De Silva, A.O.; Peart, T.E.; Cook, C.J.; Tetreault, G.R. Tissue Distribution of Substituted Diphenylamine Antioxidants and Benzotriazole Ultraviolet Stabilizers in White Sucker (*Catostomus commersonii*) from an Urban Creek in Canada. *Environ. Sci. Technol. Lett.* **2017**, *4*, 433–438. [\[CrossRef\]](#)
46. Lu, Z.; De Silva, A.O.; Peart, T.E.; Cook, C.J.; Tetreault, G.R.; Servos, M.R.; Muir, D.C.G. Distribution, Partitioning and Bioaccumulation of Substituted Diphenylamine Antioxidants and Benzotriazole UV Stabilizers in an Urban Creek in Canada. *Environ. Sci. Technol.* **2016**, *50*, 9089–9097. [\[CrossRef\]](#)
47. Montesdeoca-Esponda, S.; Álvarez-Raya, C.; Torres-Padrón, M.E.; Sosa-Ferrera, Z.; Santana-Rodríguez, J.J. Monitoring and environmental risk assessment of benzotriazole UV stabilizers in the sewage and coastal environment of Gran Canaria (Canary Islands, Spain). *J. Environ. Manag.* **2019**, *233*, 567–575. [\[CrossRef\]](#)
48. Montesdeoca-Esponda, S.; Sosa-Ferrera, Z.; Santana-Rodríguez, J.J. On-line solid-phase extraction coupled to ultra-performance liquid chromatography with tandem mass spectrometry detection for the determination of benzotriazole UV stabilizers in coastal marine and wastewater samples. *Anal. Bioanal. Chem.* **2012**, *403*, 867–876. [\[CrossRef\]](#)
49. Pei, J.; Hu, J.; Zhang, R.; Liu, N.; Yu, W.; Yan, A.; Han, M.; Liu, H.; Huang, X.; Yu, K. Occurrence, bioaccumulation and ecological risk of organic ultraviolet absorbers in multiple coastal and offshore coral communities of the South China Sea. *Sci. Total Environ.* **2023**, *868*, 161611. [\[CrossRef\]](#)
50. Serra-Roig, M.P.; Jurado, A.; Díaz-Cruz, M.S.; Vázquez-Suñé, E.; Pujades, E.; Barceló, D. Occurrence, fate and risk assessment of personal care products in river-groundwater interface. *Sci. Total Environ.* **2016**, *568*, 829–837. [\[CrossRef\]](#)
51. Song, S.; Ruan, T.; Wang, T.; Liu, R.; Jiang, G. Occurrence and removal of benzotriazole ultraviolet stabilizers in a wastewater treatment plant in China. *Environ. Sci.-Process. Impacts* **2014**, *16*, 1076–1082. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Tang, Z.; Han, X.; Li, G.; Tian, S.; Yang, Y.; Zhong, F.; Han, Y.; Yang, J. Occurrence, distribution and ecological risk of ultraviolet absorbents in water and sediment from Lake Chaohu and its inflowing rivers, China. *Ecotoxicol. Environ. Saf.* **2018**, *164*, 540–547. [\[CrossRef\]](#)
53. Vimalkumar, K.; Arun, E.; Krishna-Kumar, S.; Poopal, R.K.; Nikhil, N.P.; Subramanian, A.; Babu-Rajendran, R. Occurrence of triclocarban and benzotriazole ultraviolet stabilizers in water, sediment, fish from Indian rivers. *Sci. Total Environ.* **2018**, *625*, 1351–1360. [\[CrossRef\]](#)
54. Vimalkumar, K.; Mayilsamy, M.; Arun, E.; Gobinath, B.; Prasanth, S.; Nikhil, P.N.; Krishna-Kumar, S.; Srimurali, S.; Mkandawire, M.; Babu-Rajendran, R. Screening of antimicrobials, fragrances, UV stabilizers, plasticizers and preservatives in sewage treatment plants (STPs) and their risk assessment in India. *Chemosphere* **2022**, *308*, 136452. [\[CrossRef\]](#)
55. Wang, W.; Lee, I.-S.; Oh, J.-E. Specific-accumulation and trophic transfer of UV filters and stabilizers in marine food web. *Sci. Total Environ.* **2022**, *825*, 154079. [\[CrossRef\]](#)
56. Zhang, Z.-Y.; Xu, Y.-H.; Chen, K.-Y.; Zhang, M.-H.; Meng, C.-Y.; Wang, X.-S.; Wang, M.-M. Flower-like molybdenum disulfide/cobalt ferrite composite for the extraction of benzotriazole UV stabilizers in environmental samples. *Microchim. Acta* **2023**, *190*, 75. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Zhao, M.-L.; Chen, Y.; Yang, G.-P.; Chen, R. Simultaneous determination of benzothiazoles, benzotriazoles, and benzotriazole UV absorbers by solid-phase extraction-gas chromatography-mass spectrometry. *Environ. Sci. Pollut. Res.* **2023**, *30*, 45315–45330. [\[CrossRef\]](#) [\[PubMed\]](#)
58. Zhao, X.; Zhang, Z.-F.; Xu, L.; Liu, L.-Y.; Song, W.-W.; Zhu, F.-J.; Li, Y.-F.; Ma, W.-L. Occurrence and fate of benzotriazoles UV filters in a typical residential wastewater treatment plant in Harbin, China. *Environ. Pollut.* **2017**, *227*, 215–222. [\[CrossRef\]](#) [\[PubMed\]](#)

59. Zhang, J.; Huang, Y.; Pei, Y.; Wang, Y.; Li, M.; Chen, H.; Liang, X.; Martyniuk, C.J. Biotransformation, metabolic response, and toxicity of UV-234 and UV-326 in larval zebrafish (*Danio rerio*). *Environ. Int.* **2023**, *174*, 107896. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Liang, X.; Adamovsky, O.; Souders, C.L., 2nd; Martyniuk, C.J. Biological effects of the benzotriazole ultraviolet stabilizers UV-234 and UV-320 in early-staged zebrafish (*Danio rerio*). *Environ. Pollut.* **2019**, *245*, 272–281. [\[CrossRef\]](#)
61. Tao, J.; Bai, C.; Chen, Y.; Zhou, H.; Liu, Y.; Shi, Q.; Pan, W.; Dong, H.; Li, L.; Xu, H. Environmental relevant concentrations of benzophenone-3 induced developmental neurotoxicity in zebrafish. *Sci. Total Environ.* **2020**, *721*, 137686. [\[CrossRef\]](#)
62. Bai, C.; Dong, H.; Tao, J.; Chen, Y.; Xu, H.; Lin, J.; Huang, C.; Dong, Q. Lifetime exposure to benzophenone-3 at an environmentally relevant concentration leads to female-biased social behavior and cognition deficits in zebrafish. *Sci. Total Environ.* **2023**, *857*, 159733. [\[CrossRef\]](#)
63. Hemalatha, D.; Rangasamy, B.; Nataraj, B.; Maharajan, K.; Narayanasamy, A.; Ramesh, M. Transcriptional, biochemical, and histological alterations in adult zebrafish (*Danio rerio*) exposed to benzotriazole ultraviolet stabilizer-328. *Sci. Total Environ.* **2020**, *739*, 139851. [\[CrossRef\]](#)
64. Sandoval-Gío, J.J.; Noreña-Barroso, E.; Escalante-Herrera, K.; Rodríguez-Fuentes, G. Effect of benzophenone-3 to acetylcholinesterase and antioxidant system in zebrafish (*Danio rerio*) embryos. *Bull. Environ. Contam. Toxicol.* **2021**, *107*, 814–819. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Moreira, A.L.P.; Luchiar, A.C. Effects of oxybenzone on zebrafish behavior and cognition. *Sci. Total Environ.* **2022**, *808*, 152101. [\[CrossRef\]](#)
66. Sun, X.; Yang, Q.; Jing, M.; Jia, X.; Tian, L.; Tao, J. Environmentally relevant concentrations of organic (benzophenone-3) and inorganic (titanium dioxide nanoparticles) UV filters co-exposure induced neurodevelopmental toxicity in zebrafish. *Ecotoxicol. Environ. Saf.* **2023**, *249*, 114343. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Song, Y.; Liu, S.; Jiang, X.; Ren, Q.; Deng, H.; Paudel, Y.N.; Wang, B.; Liu, K.; Jin, M. Benzo(a)pyrene induces developmental neurotoxicity and injures exploratory, learning and memorizing abilities in zebrafish. *Sci. Total Environ.* **2022**, *834*, 155268. [\[CrossRef\]](#)
68. Huang, Y.; Law, J.C.-F.; Lam, T.-K.; Leung, K.S.-Y. Risks of organic UV filters: A review of environmental and human health concern studies. *Sci. Total Environ.* **2021**, *755*, 142486. [\[CrossRef\]](#)
69. Liang, X.; Martyniuk, C.J.; Zha, J.; Wang, Z. Brain quantitative proteomic responses reveal new insight of benzotriazole neurotoxicity in female Chinese rare minnow (*Gobiocypris rarus*). *Aquat. Toxicol.* **2016**, *181*, 67–75. [\[CrossRef\]](#)
70. Zhang, J.; Chen, H.; Tong, T.; Liu, R.; Yan, S.; Liang, X.; Martyniuk, C.J.; Zha, J. Comparative toxicogenomics of benzotriazole ultraviolet stabilizers at environmental concentrations in Asian clam (*Corbicula fluminea*): Insight into molecular networks and behavior. *J. Hazard. Mater.* **2023**, *447*, 130811. [\[CrossRef\]](#)
71. Dos Santos, B.; Ivantsova, E.; Guzman, A.P.; Martyniuk, C.J. Critical review of the toxicity mechanisms of bisphenol F in zebrafish (*Danio rerio*): Knowledge gaps and future directions. *Chemosphere* **2022**, *297*, 134132. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Ivantsova, E.; Martyniuk, C.J. A synthesis on the sub-lethal toxicity of atenolol, a beta-blocker, in teleost fish. *Environ. Toxicol. Pharmacol.* **2023**, *102*, 104236. [\[CrossRef\]](#)
73. Davis, A.P.; Wieggers, T.C.; Johnson, R.J.; Sciaky, D.; Wieggers, J.; Mattingly, C.J. Comparative Toxicogenomics Database (CTD): Update 2023. *Nucleic Acids Res.* **2023**, *51*, D1257–D1262. [\[CrossRef\]](#)
74. Zuin, M.; Rosta, V.; Trentini, A.; Bosi, C.; Zuliani, G.; Cervellati, C. Paraoxonase 1 activity in patients with Alzheimer disease: Systematic review and meta-analysis. *Chem. -Biol. Interact.* **2023**, *382*, 110601. [\[CrossRef\]](#)
75. Meyer, W.K.; Jamison, J.; Richter, R.; Woods, S.E.; Partha, R.; Kowalczyk, A.; Kronk, C.; Chikina, M.; Bonde, R.K.; Crocker, D.E. Ancient convergent losses of Paraoxonase 1 yield potential risks for modern marine mammals. *Science* **2018**, *361*, 591–594. [\[CrossRef\]](#)
76. Xu, L.; Shao, A.; Zhao, Y.; Wang, Z.; Zhang, C.; Sun, Y.; Deng, J.; Chou, L.L. Neurotoxicity of silver nanoparticles in rat brain after intragastric exposure. *J. Nanosci. Nanotechnol.* **2015**, *15*, 4215–4223. [\[CrossRef\]](#)
77. Jablonska, B.; Aguirre, A.; Vandenbosch, R.; Belachew, S.; Berthet, C.; Kaldis, P.; Gallo, V. Cdk2 is critical for proliferation and self-renewal of neural progenitor cells in the adult subventricular zone. *J. Cell Biol.* **2007**, *179*, 1231–1245. [\[CrossRef\]](#)
78. Rothhammer, V.; Borucki, D.M.; Tjon, E.C.; Takenaka, M.C.; Chao, C.-C.; Ardura-Fabregat, A.; De Lima, K.A.; Gutiérrez-Vázquez, C.; Hewson, P.; Staszewski, O. Microglial control of astrocytes in response to microbial metabolites. *Nature* **2018**, *557*, 724–728. [\[CrossRef\]](#)
79. He, T.T.; Liang, B.; Liu, W.H.; Shin, P.K.S.; Wu, R.S.S. Estrogenic potential of benzotriazole on marine medaka (*Oryzias melastigma*). *Ecotoxicol. Environ. Saf.* **2012**, *80*, 327–332.
80. Fent, K.; Chew, G.; Li, J.; Gomez, E. Benzotriazole UV-stabilizers and benzotriazole: Antiandrogenic activity in vitro and activation of aryl hydrocarbon receptor pathway in zebrafish eleuthero-embryos. *Sci. Total Environ.* **2014**, *482–483*, 125–136. [\[CrossRef\]](#)
81. Shore, E.A.; Huber, K.E.; Garrett, A.D.; Pespeni, M.H. Four plastic additives reduce larval growth and survival in the sea urchin *Strongylocentrotus purpuratus*. *Mar. Pollut. Bull.* **2022**, *175*, 113385. [\[CrossRef\]](#)
82. He, T.; Tsui, M.M.; Mayfield, A.B.; Liu, P.J.; Chen, T.H.; Wang, L.H.; Fan, T.Y.; Lam, P.K.; Murphy, M.B. Organic ultraviolet filter mixture promotes bleaching of reef corals upon the threat of elevated seawater temperature. *Sci. Total Environ.* **2023**, *876*, 162744. [\[CrossRef\]](#)
83. Apel, C.; Joerss, H.; Ebinghaus, R. Environmental occurrence and hazard of organic UV stabilizers and UV filters in the sediment of European North and Baltic Seas. *Chemosphere* **2018**, *212*, 254–261. [\[CrossRef\]](#)

84. Apel, C.; Tang, J.; Ebinghaus, R. Environmental occurrence and distribution of organic UV stabilizers and UV filters in the sediment of Chinese Bohai and Yellow Seas. *Environ. Pollut.* **2018**, *235*, 85–94. [[CrossRef](#)]
85. Avagyan, R.; Luongo, G.; Thorsen, G.; Ostman, C. Benzothiazole, benzotriazole, and their derivatives in clothing textiles—a potential source of environmental pollutants and human exposure. *Environ. Sci. Pollut. Res.* **2015**, *22*, 5842–5849. [[CrossRef](#)]
86. Carpinteiro, I.; Abuin, B.; Rodriguez, I.; Cela, R.; Ramil, M. Headspace solid-phase microextraction followed by gas chromatography tandem mass spectrometry for the sensitive determination of benzotriazole UV stabilizers in water samples. *Anal. Bioanal. Chem.* **2010**, *397*, 829–839. [[CrossRef](#)]
87. Kim, J.-W.; Ramaswamy, B.R.; Chang, K.-H.; Isobe, T.; Tanabe, S. Multiresidue analytical method for the determination of antimicrobials, preservatives, benzotriazole UV stabilizers, flame retardants and plasticizers in fish using ultra high performance liquid chromatography coupled with tandem mass spectrometry. *J. Chromatogr. A* **2011**, *1218*, 3511–3520. [[CrossRef](#)] [[PubMed](#)]
88. Li, P.; Su, W.; Liang, W.; Zhu, B.; Li, T.; Ruan, T.; Jiang, G. Occurrence and Temporal Trends of Benzotriazole UV Stabilizers in Mollusks (2010–2018) from the Chinese Bohai Sea Revealed by Target, Suspect, and Nontarget Screening Analysis. *Environ. Sci. Technol.* **2022**, *56*, 16759–16767. [[CrossRef](#)] [[PubMed](#)]
89. Li, Y.; Xing, X.; An, D.; Sun, J.; Tang, Z. Occurrence and distribution of organic ultraviolet absorbents in sediments from small urban rivers, Tianjin, China: Implications for risk management. *Ecotoxicol. Environ. Saf.* **2022**, *230*, 113120. [[CrossRef](#)]
90. Liu, R.; Ruan, T.; Wang, T.; Song, S.; Guo, F.; Jiang, G. Determination of nine benzotriazole UV stabilizers in environmental water samples by automated on-line solid phase extraction coupled with high-performance liquid chromatography–tandem mass spectrometry. *Talanta* **2014**, *120*, 158–166. [[CrossRef](#)] [[PubMed](#)]
91. Mizukawa, A.; Molins-Delgado, D.; de Azevedo, J.C.R.; Fernandes, C.V.S.; Diaz-Cruz, S.; Barcelo, D. Sediments as a sink for UV filters and benzotriazoles: The case study of Upper Iguacu watershed, Curitiba (Brazil). *Environ. Sci. Pollut. Res.* **2017**, *24*, 18284–18294. [[CrossRef](#)]
92. Molins-Delgado, D.; Díaz-Cruz, M.S.; Barceló, D. Removal of polar UV stabilizers in biological wastewater treatments and ecotoxicological implications. *Chemosphere* **2015**, *119*, S51–S57. [[CrossRef](#)] [[PubMed](#)]
93. Molins-Delgado, D.; Távora, J.; Díaz-Cruz, M.S.; Barceló, D. UV filters and benzotriazoles in urban aquatic ecosystems: The footprint of daily use products. *Sci. Total Environ.* **2017**, *601–602*, 975–986. [[CrossRef](#)]
94. Montesdeoca-Esponda, S.; Sosa-Ferrera, Z.; Kabir, A.; Furton, K.G.; Santana-Rodriguez, J.J. Fabric phase sorptive extraction followed by UHPLC-MS/MS for the analysis of benzotriazole UV stabilizers in sewage samples. *Anal. Bioanal. Chem.* **2015**, *407*, 8137–8150. [[CrossRef](#)] [[PubMed](#)]
95. Nakata, H.; Shinohara, R.-I.; Murata, S.; Watanabe, M. Detection of benzotriazole UV stabilizers in the blubber of marine mammals by gas chromatography-high resolution mass spectrometry (GC-HRMS). *J. Environ. Monit.* **2010**, *12*, 2088–2092. [[CrossRef](#)] [[PubMed](#)]
96. Tang, Z.; Zhong, F.; Cheng, J.; Nie, Z.; Han, X.; Han, Y.; Yang, Y. Concentrations and tissue-specific distributions of organic ultraviolet absorbents in wild fish from a large subtropical lake in China. *Sci. Total Environ.* **2019**, *647*, 1305–1313. [[CrossRef](#)]
97. Yao, L.; Zhao, J.-L.; Liu, Y.-S.; Yang, Y.-Y.; Liu, W.-R.; Ying, G.-G. Simultaneous determination of 24 personal care products in fish muscle and liver tissues using QuEChERS extraction coupled with ultra pressure liquid chromatography-tandem mass spectrometry and gas chromatography-mass spectrometer analyses. *Anal. Bioanal. Chem.* **2016**, *408*, 8177–8193. [[CrossRef](#)]
98. Campos, D.; Gravato, C.; Quintaneiro, C.; Golovko, O.; Žlábek, V.; Soares, A.M.V.M.; Pestana, J.L.T. Toxicity of organic UV-filters to the aquatic midge *Chironomus riparius*. *Ecotoxicol. Environ. Saf.* **2017**, *143*, 210–216. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.