QUANTITATIVE AQUATIC TOXICITY MEASURES OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS (PPCPs) AND THEIR SUBLETHAL AND LETHAL EFFECTS IN AQUATIC ORGANISMS

by

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Dedicated to my beloved wife, mother and brother for

their unwavering support and sacrifices

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ABSTRACT

Little is known about sublethal and lethal effects of exposures of PPCPs, individually or synergistically, on specific aquatic organisms. To understand the toxic implications of PPCPs on aquatic organisms, a literature review was conducted on aquatic toxicity of PPCPs. This review revealed a diverse range of aquatic organisms affected by PPCPs at both sublethal and lethal exposures, including sublethal effects at environmentally relevant concentrations. Because lethal effects were seldom observed in aquatic organisms at environmentally relevant concentrations, many studies considered PPCPs non-toxic. However, PPCP concentrations in environment will likely increase in future to sublethal and near-lethal ranges for aquatic organisms due to extensive and increasing use, except when treated through advanced wastewater treatment processes. Despite a large number of studies, few address effects of individual PPCPs on same organisms for identical exposure parameters (time, concentration), resulting in wide variation in reported toxicity levels with limited consensus in academic literature.

LIST OF ABBREVIATIONS USED

ACC	Acetyl-CoA carboxylase
AChE	Acetylcholinesterase
ALP	Alkali-labile phosphate
AOPs	Advanced oxidation processes
AMS	Amylase
CBZ	Carbamazepine
CCME	Canadian Council of Ministers of the Environment
CEPA	Canadian Environmental Protection Act
chh	Crustacean hyperglycaemic hormone
CP	Carbonyl protein
CPT1	Carnitine palmitoyl transferase
DBF	Dibenzylfluorescein dealkylase
DEET	N,N-Diethyl-meta-toluamide
Dpf	Days post fertilization
E2	Estradiol
EC50	Acute median effective concentration
ecr	Encoding ecdysone receptor
EPR	Extended product responsibility
Er	Erythrocyte count
ERA	Environmental risk assessment
EROD	Ethoxyresorufin O-deethylase
EU	European Union

FASN	Fatty acid synthase
FEQGs	Federal Environmental Quality Guidelines
GLYC	Glycogen
GPAT	Glycerol-3-phosphate acyltransferase
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione
GST	Glutathione S-transferase
Hb	Hemoglobin
20-HE	Hydroxyecdysone
HO	Heme oxidase
HPC	Hydroperoxide content
hpf	Hour post fertilization
IC50	Acute median inhibitory concentration
iNOS	NO related genes
LC50	Acute median lethal concentration
LDH	Lactate dehydrogenase
LMS	Lysosomal membrane stability
LOEC	Lowest observed effect concentration
LPO	Lipid peroxidation
LSI	Liver somatic index
MBR	Membrane bioreactor
MCHC	Mean corpuscular hemoglobin concentration

MDA	Malondialdehyde
MEC	Measured environmental concentration
MET	Mitochondrial electron transport
mih	Molt-inhibiting hormone
MTT	3(4,5-dimethyl-2-thiazholyl)-2,5-diphenyl-2H-tetrazolium bromide
MVC	Mean corpuscular volume
NADPH	Nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
NOEC	No observed effect concentration
NP	4-tert-nonylphenol
NSAIDs	Nonsteroidal anti-inflammatory drugs
OTC	Over-the-counter
PCPs	Personal care products
PEC	Predicted environmental concentration
PI	Predicted interval
PNEC	Predicted no effect concentration
POD	Peroxidase
PPCPs	Pharmaceuticals and personal care products
PROT	Protein
PSII	Photosystem system II
RQ	Risk quotient
rxr	Retinoid X receptor
SEM	Electron microscope images

SOD	Superoxide dismutase
SSA	Spontaneous swimming activity
SSDs	Species Sensitivity Distributions
TB	Trypan Blue
TEC	Total erythrocyte count
TLP	Total lipids
TST	Total swimming time
WWTPs	Wastewater treatment plants

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CHAPTER 1: Introduction

1.1 Pharmaceuticals and personal care products (PPCPs)

Pharmaceuticals and personal care products (PPCPs) comprise numerous classes of chemicals. Pharmaceuticals are defined as prescription, over-the-counter (OTC), and veterinary therapeutic drugs, which are used to treat human and animal diseases, whereas personal care products (PCPs) are used primarily to enhance the quality of daily life (Boxall et al., 2012). Pharmaceuticals include different categories of drugs such as antibiotics, antihypertensives, antiepileptics, anti-inflammatory drugs, and analgesics. PCPs include fragrances, moisturizers, lipsticks, shampoos, toothpastes, detergents, surfactants, and disinfectants (Boxall et al., 2012; Bu et al., 2013; Zhang et al., 2017).

1.2 Overview of the problem

In the last three decades, studies of the impacts of chemical pollution have focused almost solely on conventional pollutants, such as acutely toxic/carcinogenic pesticides and industrial intermediates released into the environment through wastewater effluents (Daughton & Ternes, 1999). However, another diverse group of bioactive chemicals, which have received comparatively little attention as potential and emerging environmental pollutants, include PPCPs (Daughton & Ternes, 1999). In the last decade, the development of analytical methods has made it possible to detect PPCPs at trace concentrations (e.g., ng/L) in the environment (Ternes & Joss, 2007; Wilkinson et al., 2017).

PPCPs are extensively used throughout the world and the escalating introduction of new PPCPs to the marketplace is causing exponential additions to this large array of chemicals (Daughton & Ternes, 1999). PPCPs and their metabolites are introduced to the

aquatic environments as complex mixtures through multiple routes but primarily via untreated sewage, wastewater treatment plants (WWTPs), and landfill leaching (Daughton & Ternes, 1999). Considerable quantities of PPCPs enter aquatic ecosystems due to inefficient removal by conventional wastewater treatment processes (Osorio et al., 2016). Therefore, PPCPs are regularly detected in reclaimed surface water at concentrations ranging from ng/L to μg/L (Chen et al., 2013). PPCPs are released into sewerage systems from human excretion, following internal use (e.g., ingestion) (Boxall et al., 2012). PPCPs are released into the environment from their manufacturing facilities in the form of wastewater effluent, which directly goes into WWTPs (Fick et al., 2009). PPCPs may also enter the environment through improper disposal of unused and expired drugs. Common practices of disposing of medication include flushing down the toilet, washing away in the sink, and disposing of as household trash. Washing down the toilet or sink releases PPCPs into wastewater treatment systems (Glassmeyer et al., 2009). The externally applied PCPs are washed off through shower waste, bathing, swimming, and washing sinks and enter WWTPs, from where they are released into aquatic environments (Peck, 2006). Veterinary drugs are released into aquatic environments from agricultural runoff, where animal waste is sprayed as fertilizers (La Farre et al., 2008). Moreover, the aging population, population growth, urbanization, and efficient delivery of health services are contributing to the substantial release of PPCPs into the water bodies (Brooks, 2014). Thus, there are a variety of routes through which PPCPs enter the environment (Fig. 1.1).

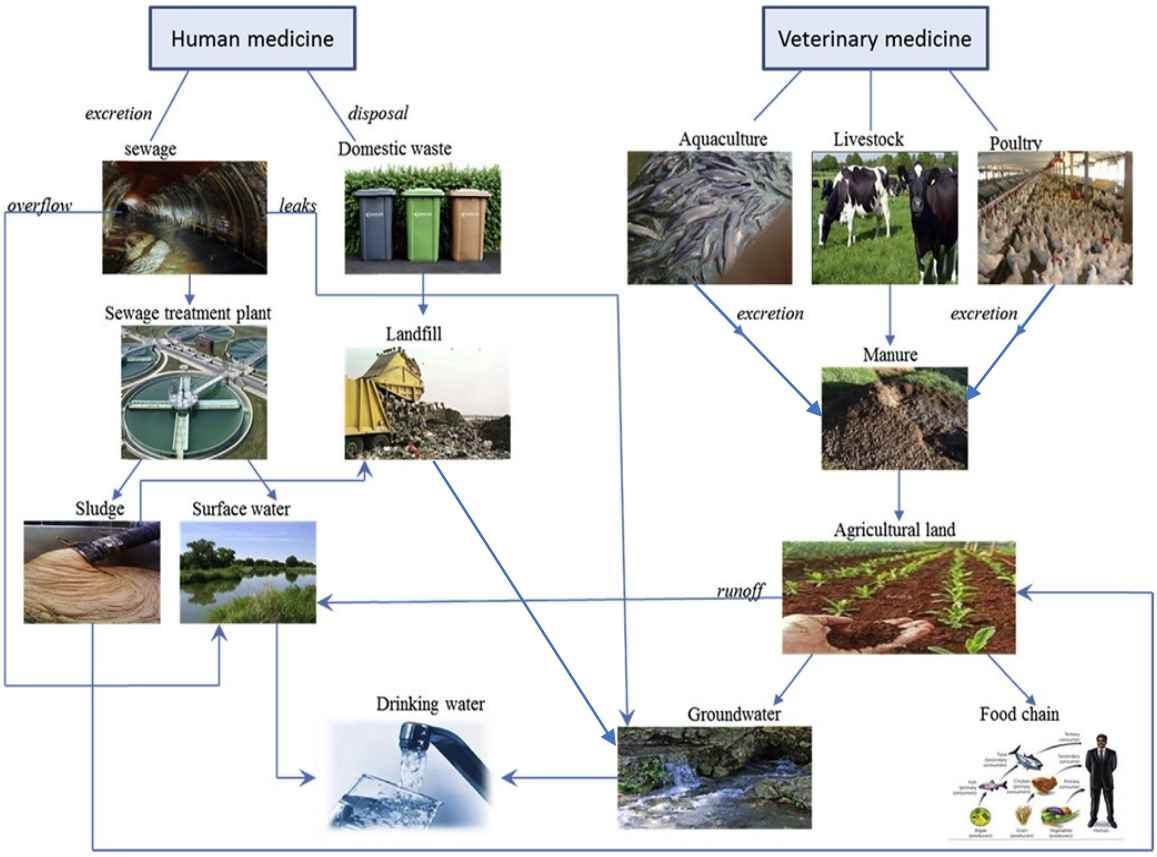

Figure 1.1. Illustration of different routes of entry of PPCPs into the environment (adapted from Ebele, Abou-Elwafa Abdallah & Harrad, 2017).

Many of these chemicals discharged in treated wastewater are pseudo-persistent due to their continuous introduction through domestic/industrial wastewater systems and runoff during wet weather, despite their environmental degradation (Daughton & Ternes, 1999). This poses risks to aquatic life because these chemicals cause acute ecotoxicity, genotoxicity, development of pathogen resistance, and endocrine disruptions in aquatic organisms (Rosal et al., 2010). PPCPs and their metabolites are biologically active and can impact non-target organisms, despite being detected at low concentrations in aquatic ecosystems (Ebele et al., 2017). Pharmaceuticals are specifically designed to produce maximum biological activity at low doses. They interact with specific enzymatic, metabolic, or cell-signalling mechanisms in target organisms to produce the desired

therapeutic effects (Fabbri & Franzellitti, 2016). The evolutionary conservation of these molecular targets in certain species potentially increases the possibility of pharmaceuticals being pharmacologically active in non-target organisms. This mode-of-action theory applies to all aquatic biota, exposed to pharmaceuticals in their natural environment. Thus, the pharmacological activity of pharmaceuticals in non-target species due to the conservation of molecular targets raises the risk of ecotoxicological effects on aquatic organisms exposed to PPCPs present in the environment (Gunnarsson et al., 2008). PPCPs affect specific functions in aquatic organisms, including development, growth, and reproduction at environmentally relevant concentrations (Franzellitti et al., 2015).

PPCPs have the potential for bioaccumulation in organisms at different trophic levels (Mackay & Barnthouse, 2010). Bioaccumulation is a process of contaminants entering into the food chain from all possible exposure routes (water, sediment, soil, air, or diet) and accumulating in biological tissues of aquatic organisms, and is expressed as a bioaccumulation factor (Wang & Fisher, 1999). For example, carbamazepine, an antiepileptic drug, accumulates in *Pseudokirchneriella subcapitata* (algae) and *Thamnocephalus platyurus* (crustacean) with bioaccumulation factors of 2.2 and 12.6, respectively (Vernouillet et al., 2010). Oxazepam, a psychiatric drug, accumulates in *Perca fluviatilis* (Eurasian perch) with a bioaccumulation factor of 12. This results in an increase in activity and feeding rate and a decrease in social behaviour of perch (Brodin et al., 2014). PPCP bioaccumulation can interfere with the endocrine system of aquatic organisms to generate undesired effects/disruption of homeostasis (Ebele et al., 2017). Toxicity also arises due to synergistic interactions when PPCPs are present as a mixture at low concentrations. For example, when in combination, carbamazepine and clofibric acid

(lipid-lowering agent) exhibited much stronger effects on *Daphnia magna* than expected from measured effects of single compounds at same concentrations. Individual concentrations of clofibric acid and carbamazepine cause 1% and 16% of immobilized daphnids, respectively. However, when both are present in a mixture at the same individual concentrations, it causes 95% of immobilized daphnids (Cleuvers, 2003). Thus, the presence of PPCPs in aquatic environment is of major ecological concern.

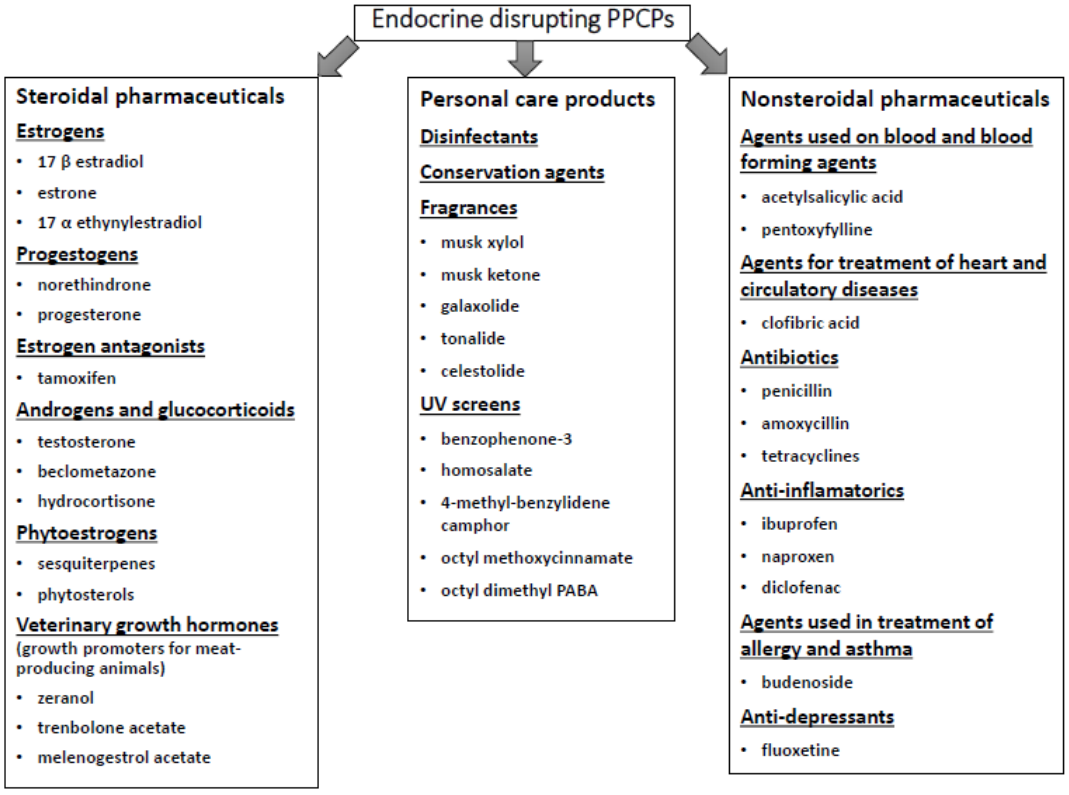

Figure 1.2. Summary of endocrine disrupting PPCPs (adapted from Ebele et al., 2017).

Although a significant amount of research has been conducted to identify the occurrence, fate, effects, and risk associated with PPCPs in the environment, a considerable amount of work remains to assess toxicity and manage the environmental risks associated with these chemicals. Thus, the focus of this thesis research is to investigate the reported impacts of PPCPs on organisms of various toxicity levels of

PPCPs in aquatic ecosystems, discover area of consensus and research gaps, and provide recommendations to mitigate levels of PPCPs in aquatic environment.

1.3 Background to the study

1.3.1 A review of the global problem

PPCPs are regularly detected in aquatic environments throughout the world. They are of ecological concern because some PPCPs are produced and used in large quantities, and it has been found through investigations that many of them cannot be degraded during wastewater treatment processes (Ashton, Hilton & Thomas, 2004). For example, in a study conducted in Montana, USA, Miller and Meek (2006) examined the presence of PPCPs in groundwater. They detected pharmaceuticals such as atrazine, carbamazepine, dilantin, diclofenac, and sulfamethoxazole with maximum concentrations of 130, 420, 22, 46 and 490 ng/L, respectively. In samples collected from untreated wastewater used for irrigation in Tula Valley, Mexico, Gibson et al. (2010) detected nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, and diclofenac ranging from 742–1406, 7267–13589 and 2052–4824 ng/L, respectively.

In the UK, drugs like mefenamic acid, diclofenac, erythromycin, propranolol, trimethoprim, and acetyl sulfamethoxazole were detected in samples collected from sewage effluents and surface waters (Hilton & Thomas, 2003). In China, a study was conducted in the Pearl River Delta to examine the concentrations and distributions of selected fluoroquinolones (antibiotics) including ciprofloxacin, enrofloxacin, and norfloxacin. Nine kinds of fish species were collected from six sites in two marine aquaculture regions for analysis; accumulation of fluoroquinolones was reported in *Siganus fuscescens*, *Sparus microcephalus,* and *Lutianus argentimaculatus* at concentrations of 255, 133 and 5 ng/g net weight, respectively, with concentrations higher

in liver than in muscle tissue (He et al., 2012). PCPs such as musk xylene and musk ketone were detected in 100% and 80%, respectively of 74 samples collected from Tama River and Tokyo Bay in Japan. These samples include three freshwater fish (e.g., *Cyprinus carpio*), four marine shellfish (e.g., *Mytilus edulis*), river water, and wastewater from three WWTPs (Yamagishi et al., 1983). In South Africa, a study conducted in surface water of the Umgeni river reported the presence of pharmaceuticals such as erythromycin, chloramphenicol, nalidixic acid, tetracycline, sulfamethoxazole, acetaminophen, atenolol, diclofenac, ibuprofen, and caffeine. Among the analytes studied in wastewater, caffeine displayed the highest average concentration at 61 ±5 (mean ±SD) ug/L and nalidixic acid being the most abundant antibiotic at 31 ±3 (mean ±SD) ug/L concentration (Agunbiade & Moodley, 2014). In watersheds of South-East Queensland, Australia, 28 antibiotics were detected in effluents from three hospitals, five wastewater treatment plants (WWTPs), six rivers, and a drinking water storage catchment. Antibiotics like β-lactam, quinolone, and sulphonamide groups were dominant in hospital effluent ranging from 0.01–14.5 μg/L (Watkinson et al., 2009). Triclosan, a commonly used antimicrobial agent in PCPs, was detected ranging from 23 to 434 ng/L in effluent samples collected from 19 WWTPs across Australia (Ying & Kookana, 2007).

1.3.2 PPCPs in aquatic environment of Canada

A study was conducted to examine the presence of prescription and non-prescription drugs in effluents of WWTPs across Canada (Metcalfe et al., 2003). Samples of wastewater were collected before and after treatment from 18 WWTPs and four sewage treatment lagoons located in 14 municipalities across five provinces of Canada. Samples were collected from WWTPs located in major cities (population >500,000), including Vancouver, Calgary, Winnipeg, Toronto, and Montreal. Pharmaceuticals like

carbamazepine, gemfibrozil (lipid regulator), and diclofenac were detected at a maximum concentration of 2.3, 1.3 and 1.3 μg/L, respectively. In another study, naproxen was detected in the range of 22–107 ng/L and clofibric acid (metabolite of lipid regulating drug clofibrate) at 103 ng/L in surface water samples collected from Detroit River at Windsor, Ontario (Boyd et al., 2003). NSAIDs like ibuprofen and naproxen and keratolytic drugs like salicylic acid were detected in samples collected from wastewater of WWTPs and surface waters near WWTP outfalls in different locations on the west coast of Vancouver Island, British Columbia (BC) (Verenitch, Lowe & Mazumder, 2006). In 2001, under the Canadian Environmental Protection Act, triclosan was selected for screening level risk assessment. Samples were collected from 44 sites across Canada between July 2012 and March 2018. Triclosan was detected at concentrations ranging from less than 6 to 874 ng/L in 226 of 918 samples. Concentrations detected in three samples collected from Wascana Creek (downstream), Saskatchewan, were above the Federal Environmental Quality Guidelines of 470 ng/L signifying a potential risk in aquatic environment (Lalonde et al., 2019). Thus, different categories of PPCPs were detected at various concentration levels in aquatic ecosystems across different jurisdictions in Canada, as well as in the world.

1.4 Research objectives

This thesis focuses on understanding the potential impacts of PPCPs in the aquatic ecosystems by examining the aquatic toxicity of PPCPs. The results produced in this thesis will support the hypothesis that the presence of PPCPs in the aquatic environment is of serious ecological concern. Specifically, the objectives of this study are to:

1. Identify aquatic organisms known to be affected by the presence of PPCPs, as reported in scientific literature;

2. Determine known thresholds of sublethal and lethal effects of PPCPs on aquatic organisms, as reported in the scientific literature; and,
3. Provide recommendations to mitigate the presence and adverse effects of PPCPs in aquatic environments.

1.5 Methodological approach

To conduct this research, a literature review was conducted to compile and identify reported sublethal and lethal toxicity levels of PPCPs for aquatic organisms. Initially, various scholarly databases were explored to reveal papers relevant to understanding the broad context and implications of occurrence of PPCPs in aquatic environments. A subset of specific PPCPs was carefully selected from the most relevant studies for extensive literature review and analysis. Search terms comprised of combinations of specific keywords, including the names of selected PPCPs, were used to identify relevant scientific articles from bibliographic databases. Revealed articles were selected and reviewed to determine the range and consistency of reported levels of sublethal and lethal toxicity for selected PPCPs. A detailed description of this methodology is provided in chapter 2.

1.6 Thesis organization

This thesis consists of three chapters, including the introduction. In chapter 2, a systematic literature review focusing on the aquatic toxicity of PPCPs is presented. It documents the variety of aquatic organisms reported as affected by the presence of PPCPs and compares the ranges and consistencies of concentrations for observed sublethal and lethal effects of specific PPCPs on specific aquatic organisms. The chapter has been submitted (June 07, 2020) as a manuscript to Environmental Reviews, co-authored by Dr. Karen F. Beazley and Dr. Tony R. Walker, and the first feedback has been received

requesting revision. Because it is intended for publication and therefore must stand alone, there is some overlap with Chapters 1 and 3. Finally, chapter 3 provides high level conclusions associated with the findings and management implications, including recommendations for mitigating concentrations of PPCPs in aquatic environments.

CHAPTER 2: A systematic literature review of the aquatic toxicity of PPCPs and their sublethal and lethal effects in aquatic organisms

2.1 Introduction

Pharmaceuticals and personal care products (PPCPs) include prescription and over-the-counter therapeutic drugs, veterinary drugs, fragrances, and cosmetics (United States Environmental Protection Agency [US EPA, 2012). They are extensively used by humans for personal health or cosmetic reasons, in agribusiness, and in veterinary medicine to boost growth or health of livestock (Halling-Sørensen et al., 2000). With their release into the environment, PPCPs are emerging as contaminants of concern. Among the so-called 'emerging' contaminants, PPCPs are considered the most important group (Mcbride & Wyckoff, 2002). It is partly due to the shift in focus of environmental contaminant research from conventional priority pollutants (e.g., polychlorinated biphenyls and polycyclic aromatic hydrocarbons) to the so-called emerging contaminants (Erickson, 2002; Field, Johnson & Rose, 2006; Arp, 2012). However, due to their relatively recent emergence, little is known about the lethal and sublethal effects of PPCPs, individually and synergistically, on specific organisms and in aquatic environments.

2.1.1 Risk of PPCPs in the aquatic environment

In recent years, PPCPs have been detected in various components of the aquatic environment, typically at ultra-low concentrations in nanograms/litre (ng/L) range (Wilkinson et al., 2017). PPCPs are released into the aquatic environment through several pathways. Major entry pathways are from WWTPs and landfill leaching (Daughton & Ternes 1999; Thomas & Hilton, 2004). Typically, WWTPs fail to remove most PPCPs, resulting in their release into treated effluents (Ternes, 1998; Hilton & Thomas, 2003).

Hence, many PPCPs pass through WWTPs and enter aquatic ecosystems in the form of parent compounds, metabolites, and transformation products (Benotti & Brownawell, 2009). Presence of PPCPs in aquatic environments leads to major concerns and can affect aquatic life through persistence, bioaccumulation, and toxicity (World Health Organisation, 2015).

Persistence - PPCPs are not easily removed by conventional wastewater treatment due to their physicochemical properties (Snyder, 2008). PPCPs thereby make their way into aquatic environments, posing a potential risk to aquatic organisms (Bu et al., 2013). Extensive use of PPCPs globally and the growing introduction of new PPCPs to the market are contributing to their increase in aquatic environments (Daughton & Ternes, 1999). Many PPCPs are pseudo-persistent in aquatic environment because they are continuously replenished by their source, despite on-going environmental degradation processes such as biodegradation, photodegradation, and particulate sorption (Houtman et al., 2004; Richmond et al., 2017).

Bioaccumulation - PPCPs and their metabolites are biologically active and have the tendency to bioaccumulate in non-target organisms in aquatic environments (Ebele et al, 2017). For example, *Gambusia holbrooki* (mosquito fish) bioaccumulated pharmaceuticals such as caffeine, diphenhydramine, diltiazem, carbamazepine, and ibuprofen by factors of 2, 16, 16, 1.4 and 28, respectively (Wang & Gardinali, 2013). Triclocarban and triclosan, widely used antimicrobial agents in PCPs, were detected in algal samples taken from effluents of WWTPs in Texas; the bioaccumulation factor for triclocarban and triclosan ranged from 1600-2700 and 900-2100, respectively (Coogan et al., 2007).

Toxicity - A major concern about the toxic implications of PPCPs arises from their ability to interfere with the endocrine system of aquatic organisms and produce undesired effects including disruption of homeostasis (Fabbri & Franzellitti, 2016; Ebele et al., 2017). For example, *Carassius auratus* (Goldfish) exhibited a reduction in plasma testosterone by over 50% after exposure to waterborne gemfibrozil for 14 days (Mimeault et al., 2005). Endocrine disrupting PPCPs include glucocorticoids, veterinary growth hormones, non-steroidal pharmaceuticals, and fragrances (Ebele et al., 2017). Further, synergistic interactions of PPCPs in a mixture lead to toxic effects, even though individual PPCPs may be present at low concentrations (Choi et al., 2008). For example, estradiol (E2) and 4-tert-nonylphenol (NP) can synergistically induce production of vitellogenin protein in juvenile rainbow trout, although neither compound does so on its own (Thorpe et al., 2001). Overall, toxicity of PPCPs depends on factors such as the sensitivity of exposed organisms, duration of exposure, contaminant concentrations, and developmental stage of the organism when exposure occurs. Exposure of non-target organisms to chronic trace levels of PPCPs at certain sensitive stages of development produces more observable abnormalities than acute exposures to high doses (Wilkinson et al., 2016).

Due to their persistence, bioaccumulation, and toxicity, occurrence of PPCPs in aquatic environments is of serious ecological concern. Knowledge is developing around the effects of PPCPs and the sublethal and lethal concentrations that trigger them, resulting in a plethora of published studies emerging in recent decades. However, it remains unclear whether there is strong scientific understanding and consensus about the various sublethal and lethal concentrations and individual and synergistic effects for many PPCPs in aquatic environments. A synthesis of the scientific literature is warranted to compile reported findings related to these factors for PPCPs. Such a review will serve

to identify the ranges of reported sublethal and lethal concentrations of specific PPCPs causing observable effects in non-target aquatic organisms, and assess the state of agreement (or lack thereof) within the scientific community on reported values for specific PPCPs in particular non-target aquatic organisms.

2.1.2 Literature review on aquatic toxicity of PPCPs

To understand the toxic implications of PPCPs on non-target aquatic organisms, a systematic literature review was conducted on aquatic toxicity of PPCPs. This review focused on identifying priority PPCPs; aquatic organisms known to be affected by presence of PPCPs in the environment; and, concentrations of PPCPs reported as producing sublethal and lethal effects in aquatic organisms. These findings serve to synthesize scientific knowledge and increase our understanding of the known quantitative measures of toxicity caused by PPCPs in aquatic organisms. Such measures will support future research and other initiatives to determine the extent and magnitude of concentrations and effects of PPCPs in aquatic environments.

This chapter describes results of this systematic literature review and discusses them in the context of the literature. Methods describe how priority PPCPs were selected for review and search terms used, steps undertaken in a systematic search and review of published studies on aquatic toxicity of PPCPs, including analytical procedures. Results highlight aquatic organisms reported as affected by the presence of PPCPs, and sublethal and lethal effects exhibited by specific aquatic organisms on exposure to PPCPs at specific concentrations through laboratory-based studies and at environmentally relevant concentrations. Results are interpreted, highlighting areas of agreement and disagreement, and identifying major research gaps. Recommendations are provided for managing

presence, concentrations, and effects of PPCPs in aquatic environments, concluding with a synthesis of key outcomes of this research.

2.2 Methods

The literature search and review entailed a series of scoping processes, representing a 'prioritization approach' (Wiegers, 1999). First, scholarly databases such as *Science Direct*, *Web of Science, Scopus,* and *Google Scholar* were explored to reveal papers relevant to understanding the broad context and implications of occurrence of PPCPs in the environment, with a focus on aquatic ecosystems. Second, a suite of priority PPCPs were carefully selected for more extensive literature review and analysis. Third, peer-reviewed scientific articles were systematically identified from the *Science Direct* database using search terms comprised of combinations of specific keywords, including names of priority PPCPs. Fourth, revealed papers were assessed to select quantitative measures of concentrations of priority PPCPs demonstrating sublethal and lethal effects on identified aquatic organisms. Finally, these measures were compiled and comparatively assessed for each priority PPCP by each aquatic organism or *vice versa*.

2.2.1 Prioritization approach

Three seminal studies provided a broad understanding about the implications of the occurrence of PPCPs in the environment, with a focus on aquatic ecosystems. These include: (1) 'Pharmaceuticals and Personal Care Products in the Environment: What Are the Big Questions?' (Boxall et al. 2012); (2) 'Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment' (Ebele et al., 2017); and, (3) 'The relative risk and its distribution of endocrine disrupting chemicals, pharmaceuticals and personal care products to freshwater organisms in the Bohai Rim, China' (Zhang et al., 2017).

From these and other publications, more than 4000 pharmaceuticals were in use by 2017, and many additional chemicals were present in personal care products. Of these, a subset of PPCPs were reported as more widely distributed in measurable concentrations and posing increased risks in aquatic environments (Ebele et al., 2017; Zhang et al., 2017). Accordingly, a prioritization approach (Wiegers, 1999) was used to identify a subset of specific 'priority PPCPs' likely to pose a greater risk to the aquatic environment based on known toxicological predictions.

2.2.2 Selection of priority PPCPs

A broad search of scientific bibliographic databases revealed 79 published papers on PPCPs in aquatic environments. Five studies were selected from which to identify a list of priority PPCPs for this review (Ebele et al., 2017; Meador et al., 2017; Zhang et al., 2017; Ellis, 2008; Guerra et al., 2014). These five studies provided the most relevant and comprehensive information about the occurrence and fate of PPCPs that cause adverse effects in aquatic ecosystems. Three of these studies provided a list of PPCPs (Table 2.1) posing risk of toxicity in aquatic environments (Ebele et al., 2017; Meador et al., 2017; Zhang et al., 2017) and, along with two others (Ellis, 2008; Guerra et al., 2014), explained the associated risks (e.g., persistence and bioaccumulation). Most of these studies focused on adverse effects of PPCPs on freshwater aquatic organisms. However, Meador et al. (2017) focused on adverse effects in marine fish, which they considered to capture exposure from both freshwater and marine sources. These five studies revealed 110 pharmaceuticals and 13 PCPs of potential concern in aquatic environments (Appendix A/Table A.1).

While finalizing priority PPCPs for review, preference was given to PPCPs that were known to be toxic to aquatic organisms (e.g., carbamazepine, sulfamethoxazole, and

triclosan). Three of the five studies contributed directly to the list of priority PPCPs toxic to specific aquatic organisms for this study. Toxic compounds selected for the priority list were supported by evidence of producing toxicity in aquatic organisms in laboratory-based studies or at environmentally relevant concentrations of PPCPs (Ebele et al., 2017; Meador et al., 2017; Zhang et al., 2017). Only toxic compounds supported by evidence of causing toxicity in aquatic organisms were selected from Ebele et al. (2017) (Appendix A/Table A.1). Compounds listed from Ellis (2008) and Guerra et al. (2014) were reported to pose risks to aquatic organisms but were not supported by evidence of toxicity and therefore not included in the final list of priority PPCPs.

A framework for identifying priority PPCPs as the focus for this review was developed based on the relationship between toxic compounds, identified in three studies (Ebele et al., 2017; Meador et al., 2017; Zhang et al., 2017) (Fig. 2.1). Toxic PPCPs identified in Ebele et al. (2017) and also found in either Meador et al. (2017) or Zhang et al. (2017) were selected. One priority PPCP, linear alkylbenzene sulfonate, is an exception to this rule; although it was listed solely in Zhang et al. (2017), it poses a hundred-fold higher risk than any of other pharmaceuticals examined by Zhang et al. (2017) to freshwater aquatic organisms, and thus is directly relevant to this study.

Through this process 12 priority PPCPs, including eight pharmaceuticals and four personal care products, were identified from these three studies, as PPCPs commonly considered to be of concern in aquatic environments (Table 2.1). Eight priority pharmaceuticals were carbamazepine, erythromycin, fluoxetine, metoprolol, naproxen, ofloxacin, sertraline, and sulfamethoxazole; and four personal care products were bisphenol A, linear alkylbenzene sulfonate, nonylphenol, and triclosan.

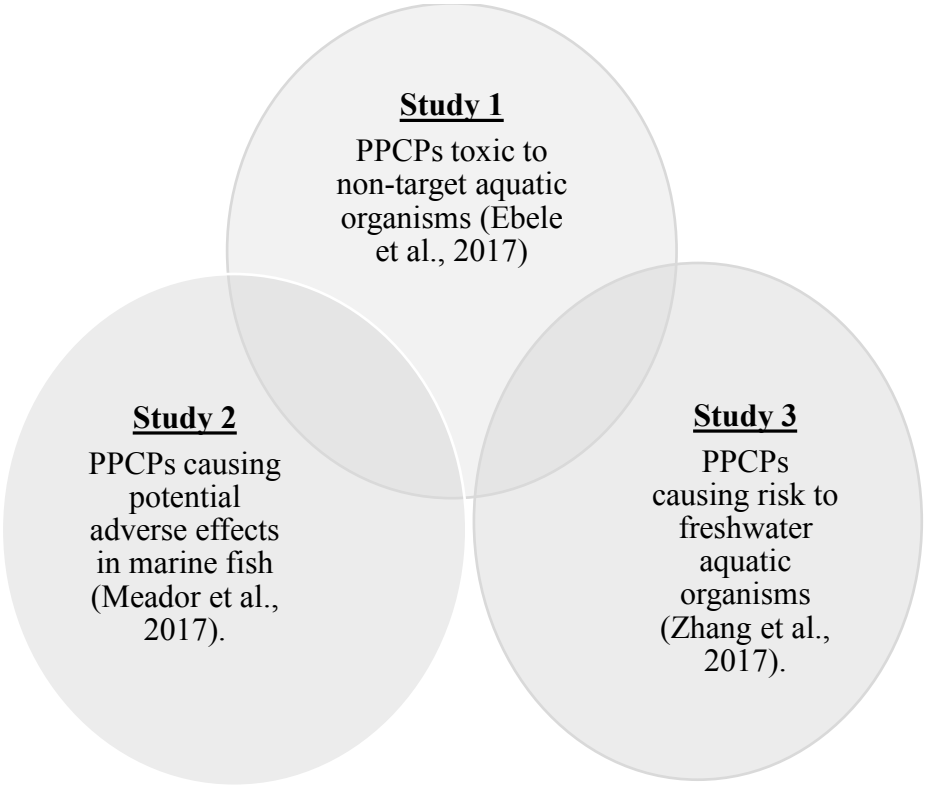

Figure 2.1. Framework for selecting priority PPCPs.

Table 2.1. PPCPs in aquatic ecosystems identified in three key studies for relative risk, adverse effects, and toxicity to aquatic organisms. Twelve priority PPCPs (indicated in grey) were selected for review in this study, based on relationships between them (Fig. 2.1). PPCPs are listed alphabetically.

Ebele et al. (2017)	Meador et al. (2017)	Zhang et al. (2017)
PPCPs toxic to non-target aquatic organisms	**PPCPs causing potential adverse effects in marine fish**	**PPCPs causing risk to freshwater aquatic organisms**
Pharmaceuticals		
Erythromycin	Alprazolam	Erythromycin
Carbamazepine	Amlodipine	Carbamazepine
Fluoxetine	Fluoxetine	Atenolol
Metoprolol	Amphetamine	Metoprolol
Naproxen	Azithromycin	Naproxen
Ofloxacin	Caffeine	Ofloxacin
Sertraline	Sertraline	Norfloxacin
Sulfamethoxazole	Diphenhydramine	Sulfamethoxazole
Ampicillin	Diltiazem	
17 beta-estradiol	Desmethyldiltiazem	
Ciprofloxacin	Fluocinonide	
Cisplantin	Metformin	
Cytarabine	Norverapamil	

Diclofenac	Norfluoxetine	
Fluvoxamine	Ranitidine	
5-Fluorouracil		
Gemfibrozil		
Ibuprofen		
Oxolinic acid		
Oxytetracycline		
Propranolol		
Sulfadimethoxine		
Tetracycline		
Trimethoprim		
Personal care products		
Bisphenol A	N,N-Diethyl-meta-toluamide (DEET)	Bisphenol A
Nonylphenol	Triclocarban	Nonylphenol
Triclosan	Triclosan	Diethylhexyl phthalate
		Linear alkylbenzene sulfonate

2.2.3 Review structure for priority PPCPs

Peer-reviewed scientific articles were systematically identified from the *Science Direct* database using search strings comprised of combinations of three specific keywords: “Aquatic”, “Toxicity”, and the name of the priority PPCP (e.g., “carbamazepine”, “erythromycin”, and “sulfamethoxazole”). The date range for the search was from 1981 to 2019. Articles revealed through initial searches were too numerous (e.g., 2042 for carbamazepine, 1251 for erythromycin, and 1947 for sulfamethoxazole), and therefore an advanced search was undertaken such that keywords searches were restricted to the title, abstract or author-specified keywords. Papers revealed through the advanced search were examined to identify research and review articles (n=408). Abstracts and conclusions of each were reviewed to assess their relevance to the research objectives based on the presence of information on:

1. Aquatic organisms affected by the presence of PPCPs in the aquatic environment;
2. Sublethal/non-lethal concentrations and effects of PPCPs on aquatic organisms;

3. Lethal concentrations specific to EC50, IC50, and LC50; and/or,
4. Risk calculation/prediction of PPCPs in the aquatic environment.

Articles were read carefully and other relevant papers identified in their references were also reviewed. A total of 404 articles including 347 initially identified plus an additional 57 selected from their references were included for analysis.

2.2.4 Identification of aquatic organisms affected by PPCPs

Articles were also reviewed to identify specific aquatic organisms noted as being measurably affected by presence of PPCPs in aquatic environments, whether studies were laboratory- or field-based. Scientific names of identified aquatic organisms, along with associated number of studies conducted for each of the 12 priority PPCPs, were tabulated. Organisms were classified into five kingdoms (i.e., Animalia, Bacteria, Fungi, Plantae, and Protista) and respective phyla (Table 2.4). Organisms were then ranked by numbers of studies conducted on effects after exposure to 12 priority PPCPs (Table 2.5).

2.2.5 Identification of sublethal and lethal effects of PPCPs

Sublethal and lethal effects produced by 12 PPCPs in aquatic organisms were identified from 404 reviewed publications. Sublethal effects include identified toxic effects of PPCPs on aquatic organisms after exposure to environmentally relevant concentrations in the field- or laboratory-based studies. These effects alter normal development, growth, and reproduction in aquatic organisms (Franzellitti et al., 2015). Lethal effects include identified lethal concentrations from laboratory-based studies. Lethal concentrations can cause immobilization, inhibition of growth or death of the exposed aquatic organisms (Ros et al., 2018). EC50, IC50, and LC50 are subcategories of lethal concentrations and are included, along with sublethal concentrations, in this review (Table 2.2).

Table 2.2. Definitions of sublethal and lethal concentrations, predicted environmental concentrations, and risk quotients for specific aquatic organisms, compiled and comparatively assessed.

EC50: Acute median effective concentration. EC50 is the concentration of drug or toxicant that produces a 50% immobilization of organisms (Definition of Toxicological Dose Descriptors, 2016a).
IC50: Acute median inhibitory concentration. IC50 is the concentration of drug or toxicant that produces a 50% inhibition in growth/growth rate of algae (Geiger, 2014).
LC50: Acute median lethal concentration. LC50 is the concentration of drug or toxicant required to kill 50% of the population (Measures of toxicity, 2020).
NOEC: No observed effect concentration. NOEC is the highest tested concentration of the drug or toxicant, at which it does not produce a statistically significant effect, different from the control. It is obtained from toxicity studies of terrestrial and aquatic organisms (Definition of Toxicological Dose Descriptors, 2016b).
LOEC: Lowest observed effect concentration. LOEC is the lowest tested concentration of the substance at which it produces a statistically significant effect, different from the control, within a given exposure time (Quantics biostatistics, 2016).
PNEC: Predicted no effect concentration. PNEC is the concentration of a substance in any environment, below which it will most likely not produce adverse effects during a long term or short-term exposure (Chemical Risk Assessment, 2016).
PEC: Predicted environmental concentration. PEC is the indication of the expected concentration of the test substance in the environment, calculated based on the initial amount present or added to the environment, its distribution, methods of removal or degradation in the environment (Green Facts, 2020).
RQ: Risk quotient. RQ is the ratio of predicted environmental concentration of test substance to its predicted no-effect concentration for water, sediment, and biota (Hernando et al., 2006). **RQ** = PEC/PNEC a. High Risk = RQ >1 b. Low to moderate risk = RQ ≤ 1 If RQ ≤ 1, the substance is not considered to be of concern. However, if RQ > 1, measures to reduce the risk ought to be undertaken (Van Assche et al., 2018).

Out of 404 reviewed articles, 215 provided information on sublethal effects (i.e., qualitative and quantitative data) and lethal concentration values (E/I/LC50) (i.e., quantitative data). Standard deviations (SDs) were calculated for lethal concentrations,

where a minimum of three concentration values were obtained for a single organism for the same PPCP compound for the same exposure time.

2.2.6 Identification of threshold and environmentally relevant concentrations of PPCPs

Minimum concentrations of PPCPs at which aquatic organisms exhibit sublethal and lethal effects were identified as threshold concentrations (Tables 2.21 and 2.22). Ranges of environmentally relevant concentrations of PPCPs were identified from scientific literature for comparing sublethal and lethal effects identified in this review (Table 2.23).

2.2.7 Identification of water quality guidelines and environmental risk assessments

Water quality guidelines for priority PPCPs developed by Federal Minister of Environment and Climate Change Canada and Canadian Council of Ministers of the Environment were identified from scientific literature (Table 2.24). These guidelines are established for protection of aquatic life and were identified to compare the levels of concentrations of PPCPs causing sublethal and lethal effects identified in this review. It can help to estimate the extent of aquatic toxicity of PPCPs. Similarly, environmental risk assessments of priority PPCPs were studied and predicted no effect concentrations (PNECs) were identified (Table 2.25). PNECs could be extended to other jurisdictions as benchmarks for the protection of aquatic life.

2.2.8 Generation of species sensitivity distributions (SSDs)

SSD curves were generated for carbamazepine (Fig. 2.2) and triclosan (Fig. 2.3), which were among the most studied priority PPCPs for aquatic toxicity. SSDs provides an estimate of proportions of species affected by different concentrations of a chemical (Posthuma et al., 2019).

2.3 Results

Results include identification of (1) the number of reviewed articles addressing studies conducted on aquatic toxicity for each of the 12 priority PPCPs; (2) number and names of diverse aquatic organisms reported as affected by measurable concentrations of these PPCPs; and, (3) sublethal and lethal concentrations of these PPCPs reported in reviewed articles as producing effects in aquatic organisms.

2.3.1 Reporting of priority PPCPs

A plethora (n=300–3385) of scientific studies were identified for each priority PPCP from *Science Direct* using search strings (i.e., "Aquatic", "Toxicity", and names of priority PPCPs). The number of studies was reduced through an advanced search focused solely on title, abstract and author-specific keywords (Table 2.3). Larger numbers of studies on carbamazepine, sulfamethoxazole, bisphenol A, nonylphenol, and triclosan were identified in initial (n=>1500) as well as refined searches (n=>45); and few studies were identified initially (n=<800) and in refined searches (n=<20) for metoprolol, ofloxacin, sertraline, and linear alkylbenzene sulfonate.

Table 2.3. Total number of articles identified for each priority PPCPs through initial and advanced searches.

12 Priority PPCPs	Number of articles identified in initial search	Number of articles identified in advanced search
Priority pharmaceuticals		
Carbamazepine	2042	85
Erythromycin	1251	28
Fluoxetine	849	38
Metoprolol	684	12
Naproxen	1141	26
Ofloxacin	777	14
Sertraline	300	16
Sulfamethoxazole	1947	47
Priority personal care products		
Bisphenol A	3385	77
Linear alkylbenzene sulfonate	333	17
Nonylphenol	2611	73
Triclosan	1618	78

2.3.2 Aquatic organisms affected by PPCPs

Numerous (n=136) aquatic organisms were reported as affected by the presence of PPCPs by laboratory and field-based studies. Summary results are presented by taxonomic phylum and PPCP (Table 2.4) and by rank order based on numbers of publications per organism (Table 2.5). Sources used to develop Tables 2.4 and 2.5 are listed in Appendix B.

Table 2.4. Number of studies on aquatic organisms affected by 12 priority PPCPs organized by taxonomic classification of organisms and PPCPs. Taxonomic classification, organisms and PPCPs are listed in alphabetical order. '—' = No Data.

Names of taxonomic groups and aquatic organisms	Total number of studies for each aquatic organism	Total number of studies for each priority pharmaceutical on specific aquatic organisms								Total number of studies for each priority personal care product on specific aquatic organisms			
		Carbamazepine	Erythromycin	Fluoxetine	Metoprolol	Naproxen	Ofloxacin	Sertraline	Sulfamethoxazole	Bisphenol A	Linear alkylbenzene sulfonate	Nonylphenol	Triclosan
	86	31	54	14	20	15	24	52	114	35	71	68	
ANIMALIA													
Annelida													
Diopatra neapolitana	1	1	—	—	—	—	—	—	—	—	—	—	—
Hediste diversicolor	1	1	—	—	—	—	—	—	—	—	—	—	—
Limnodrilus hoffmeisteri	1	—	—	—	—	—	—	—	—	—	—	—	1
Arthropoda													
Artemia franciscana	1	—	—	—	—	—	—	1	—	—	—	—	—
Artemia salina	1	—	—	—	—	—	—	—	1	—	—	—	—
Asellus aquaticus	1	—	—	—	—	—	—	—	—	1	—	—	—
Bombina orientalis	1	—	—	—	—	—	—	—	—	—	—	1	—
Ceriodaphnia dubia	13	1	2	2	—	1	1	2	2	1	2	2	3
Cichlasoma dimerus	1	—	—	—	—	—	—	—	—	—	—	1	—
Chironomus riparius	9	1	—	—	—	—	—	—	—	6	1	2	1
Chironomus tentans	7	—	—	1	—	—	—	—	—	4	1	2	—
Corophium volutator	1	—	—	—	—	—	—	—	—	—	—	1	—
Daphnia magna	55	13	6	10	3	5	1	4	5	10	4	8	10
Daphnia pulex	3	—	—	1	—	—	—	—	—	—	—	1	1
Diaphanosoma celebensis	1	—	—	—	—	—	—	—	—	1	—	—	—
Eriocheir sinensis	1	1	—	—	—	—	—	—	—	—	—	—	—
Eurytemora affinis	1	—	—	—	—	—	—	—	—	—	—	1	—
Hyalella azteca	3	—	—	1	—	—	—	—	—	2	—	—	—
Gammarus pulex	4	1	—	1	—	—	—	—	—	1	—	—	2
Litopenaeus vannamei	1	—	1	—	—	—	—	—	—	—	—	—	—
Macrobrachium rosenbergii	1	—	—	—	—	—	—	—	—	1	—	—	—
Moina macrocopa	2	—	—	—	—	1	—	—	—	1	—	1	—
Orconectes virilis	1	—	—	—	—	1	—	—	—	—	—	—	—
Procambarus clarkii	1	—	—	—	—	—	—	—	1	—	—	—	—

Thamnocephalus platyurus	**6**	**1**	**1**	**1**	—	**1**	**1**	**1**	**1**	**1**	—	—	—
Tisbe battagliai	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
Chordata													
Ancharius fuscus	**1**	—	—	—	—	—	—	—	—	—	**1**	—	—
Carassius auratus	**3**	—	—	—	—	—	—	—	—	**2**	**1**	—	—
Carassius carassius	**1**	—	**1**	—	—	—	—	—	—	—	—	—	—
Cyprinodon variegatus	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
Cyprinus carpio	**7**	**1**	—	—	**1**	**1**	—	—	—	**1**	**2**	**1**	—
Carcinus maenas	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
Danio rerio	**43**	**9**	**2**	**9**	**2**	**1**	**1**	**3**	**5**	**12**	**1**	**6**	**9**
Gambusia holbrooki	**1**	—	—	**1**	—	—	—	**1**	—	—	—	—	—
Gobiocypris rarus	**3**	—	—	—	—	—	—	—	—	**3**	—	—	—
Lepomis gibbosus	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
Limnodynastes peronii	**1**	—	—	—	—	**1**	—	—	—	—	—	—	—
Lissotriton italicus	**2**	—	—	—	—	—	—	—	—	—	—	**2**	—
Menidia menidia	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
Misgurnus anguillicaudatus	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
Oncorhynchus mykiss	**17**	**5**	**1**	**1**	—	**1**	—	**1**	**2**	**7**	**1**	**3**	**1**
Oreochromis niloticus	**2**	—	—	—	**1**	—	—	—	—	**1**	—	—	—
Oryzias latipes	**15**	**2**	—	**3**	—	**1**	—	**1**	**1**	**5**	**1**	**6**	**2**
Pangasianodon hypophthalmus	**2**	—	—	—	—	—	—	—	—	—	—	—	**2**
Pelophylax perezi	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
Phoca vitulina	**1**	**1**	**1**	—	—	**1**	—	—	—	—	—	—	—
Pimephales promelas	**12**	—	—	**2**	—	—	—	—	—	**4**	**3**	**3**	—
Poecilia reticulata	**2**	—	—	—	—	—	—	—	—	**1**	—	**1**	—
Poecilia vivipara	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
Pseudochromis fridmani	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
Rutilus rutilus	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
Salmo salar	**2**	**1**	—	—	—	—	—	—	—	—	**1**	—	—
Salmo trutta	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
Sebastiscus marmoratus	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
Xenopus laevis	**5**	—	—	—	—	—	—	—	—	**4**	**1**	—	—
Xiphophorus hellerii	**2**	—	—	—	—	—	—	—	—	**1**	—	—	**1**
Cnidaria													
Hydra attenuata	**10**	**3**	—	—	—	**2**	—	—	**2**	**1**	**1**	—	**1**
Hydra magnipapillata	**2**	—	—	—	—	**1**	—	—	—	**1**	—	—	—
Hydra vulgaris	**3**	—	—	—	—	—	—	—	—	**3**	—	—	—
Echinodermata													
Paracentrotus lividus	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—

Strongylocentrotus nudus	1	—	—	—	—	—	—	—	—	—	—	—	1
Mollusca													
Achatina fulica	1	—	—	—	—	—	—	—	—	—	—	—	1
Corbicula fluminea	2	2	—	—	—	—	—	—	—	—	—	—	—
Crassostrea angulata	1	—	—	—	—	—	—	—	—	1	—	—	—
Dreissena polymorpha	5	1	—	1	—	—	—	—	—	—	—	1	2
Elliptio complanata	1	1	—	—	—	—	—	—	—	—	—	—	—
Haliotis diversicolor	1	—	—	—	—	—	—	—	—	—	1	—	—
Haliotis tuberculata	1	—	—	—	—	—	—	—	—	—	—	—	1
Lymnaea stagnalis	2	1	1	—	—	—	—	—	1	—	—	1	—
Marisa cornuarietis	4	—	—	—	—	—	—	—	—	4	—	—	—
Melanoides tuberculatus	1	—	—	—	—	—	—	—	—	—	—	1	—
Mytilus edulis	1	1	1	1	—	—	—	—	1	—	—	—	—
Mytilus galloprovincialis	3	2	—	—	—	—	—	—	—	—	—	—	1
Perna perna	1	—	—	—	—	—	—	—	—	—	—	—	1
Pomacea lineata	1	—	—	—	—	—	—	—	—	1	—	—	—
Potamopyrgus antipodarum	1	—	—	—	—	—	—	—	—	—	—	1	—
Physella acuta	2	—	—	1	—	—	—	—	—	1	—	—	—
Ruditapes philippinarum	4	3	—	—	—	—	—	—	—	—	—	1	—
Scrobicularia plana	3	3	—	—	—	—	—	—	—	—	—	—	—
Venerupis decussata	1	1	—	—	—	—	—	—	—	—	—	—	—
Venerupis philippinarum	1	1	—	—	—	—	—	—	—	—	—	—	—
Nematoda													
Caenorhabditis elegans	1	—	—	—	—	—	—	—	—	—	—	—	1
Platyhelminthes													
Dugesia japonica	2	1	—	—	—	—	—	—	—	—	—	1	—
Schmidtea mediterranea	1	1	—	1	—	—	—	—	—	—	—	—	—
Porifera													
Eunapius fragilis	2	—	—	—	—	—	—	—	—	1	—	1	—
Heteromeyenia sp	3	—	—	—	—	—	—	—	—	2	—	1	—
Rotifera													
Brachionus calyciflorus	9	—	1	—	—	1	1	—	1	4	2	—	1
Brachionus koreanus	1	—	—	—	—	—	—	—	1	—	—	—	—
BACTERIA													
Proteobacteria													
Aquabacterium commune	1	—	1	—	—	—	—	—	—	—	—	—	—
Escherichia coli	1	—	1	—	—	—	—	—	—	—	—	—	—
Nitrosomonas europaea	1	—	—	—	—	—	—	—	—	—	1	—	—
Pseudomonas mandelii	1	—	—	—	—	—	—	—	1	—	—	—	—

Pseudomonas putida	**6**	—	—	—	—	—	**2**	—	—	**1**	**1**	**1**	—
Vibrio fischeri	**28**	**5**	**1**	**1**	**3**	—	**4**	**1**	**10**	**4**	**1**	**1**	**2**
Firmicutes													
Enterococcus faecalis	**1**	—	—	—	—	—	—	—	**1**	—	—	—	—
Bacillus subtilis	**1**	—	**1**	—	—	—	—	—	—	—	—	—	—
Cyanobacteria													
Anabaena flos-aquae	**2**	—	**1**	—	—	—	—	—	—	—	—	—	**1**
Microcystis aeruginosa	**5**	—	—	—	—	—	**1**	—	—	—	**2**	**1**	**1**
Planktothrix agardhii	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
FUNGI													
Ascomycota													
Saccharomyces cerevisiae	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
Penicillium expansum	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
Basidiomycota													
Trametes versicolor	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
PLANTAE													
Chlorophyta													
Acutodesmus obliquus	**1**	—	—	**1**	—	—	—	—	—	—	—	—	—
Chlamydomonas reinhardtii	**4**	—	—	—	—	—	—	—	—	—	—	**1**	**3**
Chlorococcum sp	**1**	**1**	—	—	—	—	—	—	—	—	—	—	**1**
Chlorella sp	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
Chlorella vulgaris	**7**	**3**	**1**	**2**	**1**	**1**	—	**1**	**2**	—	—	**1**	—
Chlorella pyrenoidosa	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
Chlorella sorokiniana	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
Desmodesmus subspicatus	**3**	—	—	—	**1**	—	—	—	—	**2**	—	—	—
Magallana gigas	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
Monoraphidium braunii	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
Nannochloris sp	**1**	**1**	—	—	—	—	—	—	**1**	—	—	—	**1**
Pseudokirchneriella subcapitata	**26**	**6**	**5**	**4**	—	—	**2**	**3**	**6**	**5**	**3**	**4**	**5**
Scenedesmus obliquus	**5**	**1**	—	—	—	—	—	—	**1**	**1**	**1**	—	**1**
Selenastrum capricornutum	**7**	—	**2**	—	—	—	—	—	**2**	**2**	—	**2**	—
Scenedesmus acutus	**1**	—	—	**1**	—	—	—	**1**	—	—	—	—	—
Scenedesmus quadricauda	**1**	—	—	**1**	—	—	—	**1**	—	—	—	—	—
Scenedesmus vacuolatus	**1**	—	—	**1**	—	—	—	—	—	—	—	—	—
Haptophyta													
Isochrysis galbana	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
Heterokonta													
Cymbella sp	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**

Navicula sp	1	—	—	—	—	—	—	—	—	—	—	—	1
Skeletonema marinoi	1	—	—	1	—	—	—	1	—	—	—	—	—
Skeletonema costatum	1	—	—	—	—	—	—	—	—	1	—	—	—
Magnoliophyta													
Eichhornia crassipes	1	1	—	—	—	—	—	—	1	—	—	—	1
Lemna gibba	4	1	—	—	—	—	—	1	1	3	—	—	—
Lemna minor	7	—	—	2	1	—	—	—	—	1	2	1	—
Myriophyllum sibiricum	1	1	—	—	—	—	—	1	1	—	—	—	—
Pistia stratiotes	1	1	—	—	—	—	—	—	1	—	—	—	1
Potamogeton pusillus	1	1	—	—	—	—	—	—	—	—	—	—	—
Ochrophyta													
Nannochloropsis limnetica	1	—	—	1	—	—	—	—	—	—	—	—	—
Cyclotella caspia	1	—	—	—	—	—	—	—	—	—	—	1	—
Tracheophyta													
Cymodocea nodosa	1	—	—	—	—	—	—	—	—	1	—	—	—
PROTISTA													
Ciliophora													
Spirostomum ambiguum	1	—	—	1	—	—	—	—	—	—	—	—	—
Tetrahymena pyriformis	1	—	—	—	1	—	—	—	—	—	—	—	—
Tetrahymena thermophila	3	—	—	—	—	—	1	—	—	—	—	—	2

Table 2.5. Rank order of aquatic organisms from highest to lowest number of studies on effects after exposure to priority PPCPs. '—' = No Data.

Ranks of aquatic organisms	Names of aquatic organisms	Total number of studies for each aquatic organism	Total number of studies for each priority pharmaceutical on specific aquatic organisms								Total number of studies for each priority personal care product on specific aquatic organisms			
			Carbamazepine	Erythromycin	Fluoxetine	Metoprolol	Naproxen	Ofloxacin	Sertraline	Sulfamethoxazole	Bisphenol A	Linear alkylbenzene sulfonate	Nonylphenol	Triclosan
			86	31	54	14	20	15	24	52	114	35	71	68
1	*Daphnia magna*	55	13	6	10	3	5	1	4	5	10	4	8	10
2	*Danio rerio*	43	9	2	9	2	1	1	3	5	12	1	6	9
3	*Vibrio fischeri*	28	5	1	1	3	—	4	1	10	4	1	1	2
4	*Pseudokirchneriella subcapitata*	26	6	5	4	—	—	2	3	6	5	3	4	5
5	*Oncorhynchus mykiss*	17	5	1	1	—	1	—	1	2	7	1	3	1
6	*Oryzias latipes*	15	2	—	3	—	1	—	1	1	5	1	6	2
7	*Ceriodaphnia dubia*	13	1	2	2	—	1	1	2	2	1	2	2	3
8	*Pimephales promelas*	12	—	—	2	—	—	—	—	—	4	3	3	—
9	*Hydra attenuata*	10	3	—	—	—	2	—	—	2	1	1	—	1
10	*Brachionus calyciflorus*	9	—	1	—	—	1	1	—	1	4	2	—	1
10	*Chironomus riparius*	9	1	—	—	—	—	—	—	—	6	1	2	1
11	*Chironomus tentans*	7	—	—	1	—	—	—	—	—	4	1	2	—
11	*Chlorella vulgaris*	7	3	1	2	1	1	—	1	2	—	—	1	—
11	*Cyprinus carpio*	7	1	—	—	1	1	—	—	—	1	2	1	—
11	*Lemna minor*	7	—	—	2	1	—	—	—	—	1	2	1	—
11	*Selenastrum capricornutum*	7	—	2	—	—	—	—	—	2	2	—	2	—
12	*Thamnocephalus platyurus*	6	1	1	1	—	1	1	1	1	1	—	—	—
12	*Pseudomonas putida*	6	—	—	—	—	—	2	—	—	1	1	1	—
13	*Dreissena polymorpha*	5	1	—	1	—	—	—	—	—	—	—	1	2
13	*Microcystis aeruginosa*	5	—	—	—	—	—	1	—	—	—	2	1	1
13	*Scenedesmus obliquus*	5	1	—	—	—	—	—	—	1	1	1	—	1
13	*Xenopus laevis*	5	—	—	—	—	—	—	—	—	4	1	—	—
14	*Chlamydomonas reinhardtii*	4	—	—	—	—	—	—	—	—	—	—	1	3
14	*Gammarus pulex*	4	1	—	1	—	—	—	—	—	1	—	—	2
14	*Lemna gibba*	4	1	—	—	—	—	—	1	1	3	—	—	—

14	*Marisa cornuarietis*	**4**	—	—	—	—	—	—	—	—	**4**	—	—	—
14	*Ruditapes philippinarum*	**4**	**3**	—	—	—	—	—	—	—	—	—	**1**	—
15	*Carassius auratus*	**3**	—	—	—	—	—	—	—	—	**2**	**1**	—	—
15	*Daphnia pulex*	**3**	—	—	**1**	—	—	—	—	—	—	—	**1**	**1**
15	*Desmodesmus subspicatus*	**3**	—	—	—	**1**	—	—	—	—	**2**	—	—	—
15	*Heteromeyenia sp*	**3**	—	—	—	—	—	—	—	—	**2**	—	**1**	—
15	*Hyalella azteca*	**3**	—	—	**1**	—	—	—	—	—	**2**	—	—	—
15	*Hydra vulgaris*	**3**	—	—	—	—	—	—	—	—	**3**	—	—	—
15	*Gobiocypris rarus*	**3**	—	—	—	—	—	—	—	—	**3**	—	—	—
15	*Mytilus galloprovincialis*	**3**	**2**	—	—	—	—	—	—	—	—	—	—	**1**
15	*Scrobicularia plana*	**3**	**3**	—	—	—	—	—	—	—	—	—	—	—
15	*Tetrahymena thermophila*	**3**	—	—	—	—	—	**1**	—	—	—	—	—	**2**
16	*Anabaena flos-aquae*	**2**	—	**1**	—	—	—	—	—	—	—	—	—	**1**
16	*Corbicula fluminea*	**2**	**2**	—	—	—	—	—	—	—	—	—	—	—
16	*Dugesia japonica*	**2**	**1**	—	—	—	—	—	—	—	—	—	**1**	—
16	*Eunapius fragilis*	**2**	—	—	—	—	—	—	—	—	**1**	—	**1**	—
16	*Hydra magnipapillata*	**2**	—	—	—	—	**1**	—	—	—	**1**	—	—	—
16	*Lissotriton italicus*	**2**	—	—	—	—	—	—	—	—	—	—	**2**	—
16	*Lymnaea stagnalis*	**2**	**1**	**1**	—	—	—	—	—	**1**	—	—	**1**	—
16	*Moina macrocopa*	**2**	—	—	—	—	**1**	—	—	—	**1**	—	**1**	—
16	*Oreochromis niloticus*	**2**	—	—	—	**1**	—	—	—	—	**1**	—	—	—
16	*Pangasianodon hypophthalmus*	**2**	—	—	—	—	—	—	—	—	—	—	—	**2**
16	*Physella acuta*	**2**	—	—	**1**	—	—	—	—	—	**1**	—	—	—
16	*Poecilia reticulata*	**2**	—	—	—	—	—	—	—	—	**1**	—	**1**	—
16	*Salmo salar*	**2**	**1**	—	—	—	—	—	—	—	—	**1**	—	—
16	*Xiphophorus hellerii*	**2**	—	—	—	—	—	—	—	—	**1**	—	—	**1**
17	*Achatina fulica*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Acutodesmus obliquus*	**1**	—	—	**1**	—	—	—	—	—	—	—	—	—
17	*Ancharius fuscus*	**1**	—	—	—	—	—	—	—	—	—	**1**	—	—
17	*Aquabacterium commune*	**1**	—	**1**	—	—	—	—	—	—	—	—	—	—
17	*Artemia franciscana*	**1**	—	—	—	—	—	—	**1**	—	—	—	—	—
17	*Artemia salina*	**1**	—	—	—	—	—	—	—	**1**	—	—	—	—
17	*Asellus aquaticus*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—

17	*Bacillus subtilis*	**1**	—	**1**	—	—	—	—	—	—	—	—	—	—
17	*Bombina orientalis*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Brachionus koreanus*	**1**	—	—	—	—	—	—	—	**1**	—	—	—	—
17	*Caenorhabditis elegans*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Carassius carassius*	**1**	—	**1**	—	—	—	—	—	—	—	—	—	—
17	*Carcinus maenas*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Chlorella pyrenoidosa*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Chlorella sorokiniana*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Chlorella sp*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Chlorococcum sp*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	**1**
17	*Cichlasoma dimerus*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Corophium volutator*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Crassostrea angulata*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Cyclotella caspia*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Cymbella sp*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Cymodocea nodosa*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Cyprinodon variegatus*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Diaphanosoma celebensis*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Diopatra neapolitana*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Enterococcus faecalis*	**1**	—	—	—	—	—	—	—	**1**	—	—	—	—
17	*Eichhornia crassipes*	**1**	**1**	—	—	—	—	—	—	**1**	—	—	—	**1**
17	*Elliptio complanata*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Eriocheir sinensis*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Escherichia coli*	**1**	—	**1**	—	—	—	—	—	—	—	—	—	—
17	*Eurytemora affinis*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Gambusia holbrooki*	**1**	—	—	**1**	—	—	—	**1**	—	—	—	—	—
17	*Haliotis diversicolor*	**1**	—	—	—	—	—	—	—	—	—	**1**	—	—
17	*Haliotis tuberculata*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Hediste diversicolor*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Isochrysis galbana*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Lepomis gibbosus*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Limnodrilus hoffmeisteri*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Limnodynastes peronii*	**1**	—	—	—	—	**1**	—	—	—	—	—	—	—
17	*Litopenaeus vannamei*	**1**	—	**1**	—	—	—	—	—	—	—	—	—	—
17	*Macrobrachium rosenbergii*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—

17	*Magallana gigas*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Melanoides tuberculatus*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Menidia menidia*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Misgurnus anguillicaudatus*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Monoraphidium braunii*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Myriophyllum sibiricum*	**1**	**1**	—	—	—	—	—	**1**	**1**	—	—	—	—
17	*Mytilus edulis*	**1**	**1**	**1**	**1**	—	—	—	—	**1**	—	—	—	—
17	*Nannochloropsis limnetica*	**1**	—	—	**1**	—	—	—	—	—	—	—	—	—
17	*Nannochloris sp*	**1**	**1**	—	—	—	—	—	—	**1**	—	—	—	**1**
17	*Navicula sp*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Nitrosomonas europaea*	**1**	—	—	—	—	—	—	—	—	—	**1**	—	—
17	*Orconectes virilis*	**1**	—	—	—	—	**1**	—	—	—	—	—	—	—
17	*Paracentrotus lividus*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Pelophylax perezi*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Penicillium expansum*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Perna perna*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Phoca vitulina*	**1**	**1**	**1**	—	—	**1**	—	—	—	—	—	—	—
17	*Pistia stratiotes*	**1**	**1**	—	—	—	—	—	—	**1**	—	—	—	**1**
17	*Planktothrix agardhii*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Poecilia vivipara*	**1**	—	—	—	—	—	—	—	—	—	—	—	**1**
17	*Pomacea lineata*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Potamogeton pusillus*	**1**	**1**	—	—	—	—	—	—	—	—	—	—	—
17	*Potamopyrgus antipodarum*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Procambarus clarkii*	**1**	—	—	—	—	—	—	—	**1**	—	—	—	—
17	*Pseudochromis fridmani*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Pseudomonas mandelii*	**1**	—	—	—	—	—	—	—	**1**	—	—	—	—
17	*Rutilus rutilus*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Saccharomyces cerevisiae*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Salmo trutta*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Scenedesmus acutus*	**1**	—	—	**1**	—	—	—	**1**	—	—	—	—	—
17	*Scenedesmus quadricauda*	**1**	—	—	**1**	—	—	—	**1**	—	—	—	—	—
17	*Scenedesmus vacuolatus*	**1**	—	—	**1**	—	—	—	—	—	—	—	—	—
17	*Schmidtea mediterranea*	**1**	**1**	—	**1**	—	—	—	—	—	—	—	—	—
17	*Sebastiscus marmoratus*	**1**	—	—	—	—	—	—	—	—	—	—	**1**	—
17	*Skeletonema marinoi*	**1**	—	—	**1**	—	—	—	**1**	—	—	—	—	—
17	*Skeletonema costatum*	**1**	—	—	—	—	—	—	—	—	**1**	—	—	—
17	*Spirostomum ambiguum*	**1**	—	—	**1**	—	—	—	—	—	—	—	—	—

17	*Strongylocentrotus nudus*	1	—	—	—	—	—	—	—	—	—	—	—	1
17	*Tisbe battagliai*	1	1	—	—	—	—	—	—	—	—	—	—	—
17	*Tetrahymena pyriformis*	1	—	—	—	1	—	—	—	—	—	—	—	—
17	*Trametes versicolor*	1	1	—	—	—	—	—	—	—	—	—	—	—
17	*Venerupis decussata*	1	1	—	—	—	—	—	—	—	—	—	—	—
17	*Venerupis philippinarum*	1	1	—	—	—	—	—	—	—	—	—	—	—

2.3.3 Summary assessment of aquatic organisms reported to be affected by priority PPCPs

Among aquatic organisms (n=136) identified as exhibiting sublethal and lethal effects on exposure to PPCPs, certain species were more widely studied and reported. A large number of studies were identified for *Daphnia magna* (n=55), *Danio rerio* (n=43), *Vibrio fischeri* (n=28), *Pseudokirchneriella subcapitata* (n=26), *Oncorhynchus mykiss* (n=17), and *Oryzias latipes* (n=15). Among them, organisms like *Daphnia magna* and *Danio rerio* were studied for aquatic toxicity across all 12 priority PPCPs. However, some organisms were frequently studied for specific PPCP compounds, such as *Daphnia magna* for carbamazepine (n=13), *Vibrio fischeri* for sulfamethoxazole (n=10), *Danio rerio* for bisphenol A (n=12), and *Oncorhynchus mykiss* for bisphenol A (n=7). Organisms less frequently studied and reported for aquatic toxicity include *Diopatra neapolitana* (n=1), *Artemia franciscana* (n=1), *Orconectes virilis* (n=1), *Salmo trutta* (n=1), *Moina macrocopa* (n=2), and *Oreochromis niloticus* (n=2).

Some phyla of organisms were more widely studied than others, including Arthropoda, Chordata, Mollusca, and Chlorophyta. Understudied phyla of organisms were Annelida, Cnidaria, Echinodermata, Nematoda, Echinodermata, Nematoda, Platyhelminthes, Porifera, Rotifera, Proteobacteria, Firmicutes, Cyanobacteria, Ascomycota, Basidiomycota, Haptophyta, Heterokonta, Magnoliophyta, Ochrophyta,

Tracheophyta, and Ciliophora (Table 2.4). Thus, there were only a few phyla of organisms that were widely studied for sublethal and lethal effects of PPCPs.

Of the 12 priority PPCPs, the most studied for toxicity on aquatic organisms was bisphenol A (n=114); and others were carbamazepine, fluoxetine, sulfamethoxazole, nonylphenol, and triclosan (n=52–86). Compounds most infrequently studied for their toxic effects on aquatic organisms were metoprolol, naproxen, and ofloxacin (n=<20) (Tables 2.4 and 2.5).

2.3.4 Sublethal effects of PPCPs on aquatic organisms

A variety of sublethal effects are produced in aquatic organisms on exposure to PPCPs. Sublethal effects reported in reviewed studies include abnormal gamete formation (Madureira et al., 2011), embryonic deformities (Van den Brandhof & Montforts, 2010), elevation of catabolic enzymes in liver and muscle tissues (Li et al. 2011), algal growth inhibition (Liu et al., 2011), and/or reduction in swimming activity in fishes (De Lange et al., 2006). A range of sublethal effects for exposure times and concentrations of PPCPs reported in specific aquatic organisms (n=79) are presented for each of the 12 priority PPCPs (Tables 2.6–2.17).

2.3.4.1 Carbamazepine

Sublethal effects of carbamazepine on 26 aquatic organisms were reported at concentrations ranging from 0.01µg/L to 150 mg/L (equivalent to 150,000 µg/L, representing difference of up to seven orders of magnitude) and exposure times from five min to 42 d (Table 2.6). The lowest reported exposure time showing sublethal effects of carbamazepine was 5 min for ultrasensitive *Vibrio fischeri*, exhibiting significant inhibition of bacterial bioluminescence after exposure to low concentrations (i.e., 0.20-18 µg/L) (Aguirre-Martinez et al., 2015). Other reported aquatic organisms sensitive to

carbamazepine were *Carcinus maenas*, *Diopatra neapolitana*, *Eriocheir sinensis*, *Gammarus pulex*, and *Ruditapes philippinarum*. These organisms exhibited sublethal effects after exposure to low concentrations of carbamazepine, typically in the micrograms/litre (µg/L) ranges at various exposure times. Among them, *Gammarus pulex* was highly sensitive, exhibiting a significant reduction in swimming activity at ultra-low concentrations (i.e., 0.01 µg/L) after exposure for 1.5 h (De Lange et al., 2006). Organisms reported as expressing relatively low sensitivity to carbamazepine were *Danio rerio, Daphnia magna*, and *Pseudokirchneriella subcapitata*. These organisms exhibited sublethal effects after exposure to high concentrations of carbamazepine, typically in milligrams/litre (mg/L) ranges at various exposure times. For example, *Danio rerio* exhibited oedema in embryos after exposure to high concentrations (i.e., 1 mg/L) (Weichert et al., 2017). Thus, a variety of sublethal effects of carbamazepine were observed in diverse aquatic organisms after exposure to a range of concentrations and exposure times.

Table 2.6. Sublethal effects of carbamazepine.

Names of aquatic organisms	Exposure times (min/h/d)	Sublethal effects of carbamazepine on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Brachionus koreanus	12 h	Significant decrease in activity of acetylcholinesterase (AChE) after exposure to 100 and 1000 µg/L (Rhee et al., 2012).
	24 h	Significant decrease in activity of acetylcholinesterase (AChE) and relative mRNA expression after exposure to 1 mg/L (Rhee et al., 2012).
Carcinus maenas	28 d	Significant increase in activity of ethoxyresorufin O-deethylase (EROD) in hepatopancreas tissue and glutathione peroxidase (GPx) in hepatopancreas, gill, and muscle tissue after exposure to 50 µg/L. Significant increase in activity of dibenzylfluorescein dealkylase (DBF) in hepatopancreas and gill tissue after exposure to 10 and 50 µg/L. Significant increase in glutathione S-transferase (GST) in muscle and gonad tissue after exposure to 1µg/L. Significant increase in levels of lipid peroxidation (LPO) in gonad tissue after exposure to 0.1, 1, 10 and 50 µg/L (Aguirre-Martinez et al., 2013).
Chlorella pyrenoidosa	5 d/10 d	Significant decrease in chlorophyll a content after exposure to 1, 5 and 10 mg/L. Increase in activity of catalase (CAT) after exposure to 0.5, 1, 2, 5 and 10 mg/L and reflect maximum activity of catalase at 10 mg/L (Zhang et al., 2012).
Corbicula fluminea	21 d	Significant increase in levels of dopamine, total lipids (TLP), activity of arachidonic acid cyclooxygenase, and mitochondrial electron transport (MET) in gonad tissues after exposure to 0.1, 1, 10 and 50 µg/L. Significant inhibition in activity of acetylcholinesterase (AChE) in digestive gland tissues (Aguirre-Martinez et al., 2018).

		Significant increase in activity of glutathione peroxidase (GPX), levels of lipid peroxidation, and DNA damage after exposure to 0.1, 1, 10 and 50 µg/L (Aguirre-Martinez et al., 2015).
Danio rerio	48 h	Oedema in embryos after exposure to sublethal concentrations of 1, 25, 50, 75 and 100 mg/L (Weichert et al., 2017).
	72 h	Tail deformation in 2 h old embryo after exposure to 61.5 mg/L and retardation in growth above 122 mg/L (Van den Brandhof & Montforts, 2010).
	21 d	Significant reduction in spermatozoa in adults after exposure to 1.78 mg/L (Madureira et al., 2011).
Daphnia magna	48 h	Alteration of energy metabolism after exposure to 1.75–14 mg/L. Depletion in levels of amino acids such as alanine, arginine, leucine, glycine, glutamate, glutamine, proline, serine, and aromatic amino acids such as tryptophan, phenylalanine, and tyrosine (Kovacevic et al., 2016).
Diopatra neapolitana	28 d	Significant differences in regeneration capacity on day 11 and 18 after amputation in organisms exposed to 9.0 µg/L (Pires et al., 2016b).
Dreissena polymorpha	48 h	Significant reduction in viability of gill cells and digestive gland cells after exposure to 10 mg/L, measured by MTT (3(4,5-dimethyl-2-thiazholyl)-2,5-diphenyl-2H-tetrazolium bromide) reduction assay (Parolini et al., 2011).
	96 h	Significant reduction in viability of gill cells, digestive gland cells, and hemocyte cells after exposure to 0.001, 0.01, 0.1, 1 and 10 mg/L, measured by Trypan Blue (TB) exclusion test (Parolini et al., 2011).
Eriocheir sinensis	4 d	Significant decrease in activity of epidermal enzymes, including chitinase by 0.55-fold and chitobiase by 0.49-fold after exposure to 10 µg/L. Significant decrease in concentration of 20-hydroxyecdysone (20-HE) in hemolymph by 0.83 after exposure to 10 µg/L. Significant induction of transcripts of genes encoding crustacean hyperglycaemic hormone (chh) and molt-inhibiting hormone (mih) in eyestalks after exposure to 1 or 10 µg/L. Significant suppression of expressions of genes encoding ecdysone receptor (ecr) and crustacean retinoid X receptor (rxr) in hepatopancreas after exposure to 1 or 10 µg/L (Chen et al., 2019a).
Gammarus pulex	1.5 h	Significant reduction in swimming activity after exposure to 0.01 µg/L (De Lange et al., 2006).
Hediste hemolymph	28 d	Significant increase in levels of lipid peroxidation (LPO) after exposure to 3.0 and 6.0 µg/L and a significant decrease in glutathione content after exposure to 0.3, 3.0 and 6.0 µg/L. Significant decrease in activity of catalase (CAT) after exposure to 0.3, 3.0, 6.0 and 9.0 µg/L. Significant increase in activity of glutathione S-transferase (GST) after exposure to 9.0 µg/L and cytochrome P450 3A4 (CYP3A4) after exposure to 6.0 and 9.0 µg/L. Activity of electron transport system was significantly decreased after exposure to 0.3 µg/L and significantly increased after exposure to 6.0 and 9.0 µg/L (Pires et al., 2016a).
Hydra attenuata	96 h	Significant reduction in morphology and feeding behaviour after exposure to 50 mg/L (Quinn et al., 2008).
	6 h	Significant increase in activity of global cytochrome P450 and cytochrome P450 3A4 by 63% and 433%, respectively and significant reduction in lipid peroxidation by 56% after exposure to *Thamnocephalus platyurus* exposed to carbamazepine contaminated algae (*Pseudokirchneriella subcapitata* exposed to 150 mg/L for 24 h (Vernouillet et al., 2010).
Lepomis gibbosus	96 h	Significant increase in activity of glutathione reductase (GR) after exposure to 62.5 µg/L and glutathione S-transferase (GST) after exposure to 250 and 1000 µg/L (Brandao et al., 2013).
Mytilus galloprovincialis	96 h	Significant reduction in concentrations of protein content after exposure to 3.0 and 6.0 µg/L, glycogen content after exposure to 6.0 and 9.0 µg/L, and a significant increase in levels of lipid peroxidation after exposure to 9.0 µg/L. Significant increase in activity of electron transport system after exposure to 6.0 and 9.0 µg/L. Significant reduction in activity of superoxide dismutase (SOD) after exposure to 9.0 µg/L and catalase (CAT) after exposure to 6.0 and 9.0 µg/L (Oliveira et al., 2017).
	7 d	Reduction in hemocyte lysosome membrane stability by 60% and 80% after exposure to 0.1 and 10 µg/L, respectively. Significant increase in malondialdehyde (MDA) content (biomarker for lipid peroxidation) in gills after exposure to 0.1 and 10 µg/L and in mantle/gonads after exposure to 10 µg/L. Significant increase in activity of glutathione S-transferase (GST) in digestive glands after exposure to 0.1 µg/L and in mantle/gonads after exposure to 0.1 and 10 µg/L. Activity of catalase significantly increased in digestive glands after exposure to 0.1 and 10 µg/L and in mantle/gonads after exposure to10 µg/L (Martin-Diaz et al., 2009)
	28 d	Significant increase in activity of electron transport system after exposure to 3.0, 6.0 and 9.0 µg/L and a significant decrease in gonadosomatic index after exposure to 9.0 µg/L (Oliveira et al., 2017).
Oncorhynchus mykiss	24 h	Inhibition of basal activity of ethoxyresorufin-O-deethylase (EROD) in primary rainbow trout hepatocytes after exposure to a concentration ranging from 0.92–118.13 mg/L (Laville et al., 2004).
		Loss of cells, induction of cellular pleomorphism, and hydropic degeneration of cytoplasm observed in cell line RTG-2 derived from gonad of fish after exposure to 141.76 mg/L (Jos et al., 2003).
	48 h	Acceleration in rate of oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and increase in levels of lipid peroxidation in microsomal membranes of hepatocytes after exposure to 23.63 mg/L (Gagne et al., 2006).

	96 h	Increase in activities of super oxidase dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx) in the intestine, muscle, and especially in liver. Changes in hematological profile leading to an increase in erythrocyte count (Er), hemoglobin (Hb), mean corpuscular hemoglobin concentration (MCHC), monocytes, and neutrophil granulocytes. The tested concentrations were 5, 10, 15, 20, 25 and 30 mg/L (Li et al., 2011).
	21 d	Significant increase in levels of hemoglobin, ammonia, and glucose and activities of plasma enzymes after exposure to 0.2 mg/L (Li et al., 2010).
		Significant increase in levels of lipid peroxidation (LPO) and carbonyl protein (CP) and significant inhibition of activity of super oxidase dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx) after exposure to 0.2 mg/l or 2 mg/L (Li et al., 2009).
	42 d	Significant increase in levels of hemoglobin, ammonia, glucose, and plasma enzymes activities after exposure to 0.2 and 2 mg/L. Significant increase in levels of lipid peroxidation and protein carbonyl in the liver, resulting in an inability to induce antioxidant enzymes activities, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GST) after exposure to 2 mg/L (Li et al., 2010)
		Significant increase in levels of lipid peroxidation (LPO) and carbonyl protein (CP), reduction in activity of Na^+–K^+-ATPase in gill, and significant inhibition of antioxidant enzymes activities, including super oxidase dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx) after exposure to 0.2 or 2 mg/L (Li et al., 2009).
Oryzias latipes	9 d	Changes in feeding behaviour resulting in increased time to eat midge larva (TE) and a significant decrease in swimming speed on day 8 and 9 after exposure to 6.15 mg/L (Nassef et al., 2010).
Phoca vitulina	66 h	Significant suppression of immune responses through inhibition of proliferation of peripheral blood mononuclear cells after exposure to a concentration ranging from 0.50–100 mg/L (Kleinert et al., 2018).
Pseudokirchneriella subcapitata	24 h	Significant increase in activity of glutathione reductase (GR) and strong inhibition of CYP450 3A4-like activity after exposure to 150 mg/L (Vernouillet et al., 2010).
Ruditapes philippinarum	28 h	Significant increase in activity of superoxidase dismutase (SOD) after exposure to 0.03, 0.30 and 3.00 µg/L. Significant decrease in activity of catalase (CAT) enzyme after exposure to 9.00 µg/L and levels of lipid peroxidation (LPO) after exposure to 0.03, 0.30 and 9.00 µg/L (Almeida et al., 2015).
	35 d	Significant reduction by 50% in lysosomal membrane stability (LMS) after exposure to 1 µg/L (Aguirre-Martinez., 2013).
Salmo salar	5 d	Significant changes in expression of mRNA in brain after exposure to 7.85 ± 0.13 µg/L. Following exposure, 373 features were differently expressed with 26 showing up or down regulation. The highest change was observed in mRNAs for pituitary hormones encoding features somatolactin, prolactin, and somatotropin (Hampel et al., 2014).
Scenedesmus obliquus	5 d/10 d	Significant decrease in chlorophyll a content after exposure to 1, 5 and 10 mg/L. Increase in activity of catalase (CAT) after exposure to 0.5, 1, 2, 5 and 10 mg/L and reflect maximum activity of catalase at 10 mg/L (Zhang et al., 2012).
Scrobicularia plana	96 h	Significant decrease in glycogen (GLYC) content after exposure to 9.0 µg /L of irradiated carbamazepine (CBZ) and 3.0 µg/L of non-irradiated CBZ. Significant decrease in protein (PROT) content after exposure to 6.0 µg /L of irradiated CBZ. Significant decrease in levels of lipid peroxidation (LPO) after exposure to 3.0 µg /L of irradiated CBZ and an increase in levels of LPO after exposure to 9.0 µg/L of non-irradiated CBZ. The activity of superoxide dismutase (SOD) decreased significantly after exposure to 9.0 µg /L of irradiated CBZ and 6.0 and 9.0 µg/L of non-irradiated CBZ. The activity of catalase (CAT) increased significantly after exposure to 0.3, 3.0 and 6.0 µg /L of irradiated CBZ and 6.0 and 9.0 µg /L of non-irradiated CBZ (Almeida et al., 2017).
Schmidtea mediterranea	9 d	Significant increase of 23.5% and 35.5% in locomotor activity after exposure to 0.1 and 1.0 µg/L, respectively (Ofoegbu et al., 2019).
Thamnocephalus platyurus	24 h	Strong inhibition of activity of cytochrome P450 3A4, significant induction of activity of heme oxidase (HO) and glutathione S-transferase (GST), and significant reduction in lipid peroxidation by 72% after feeding with carbamazepine exposed algae (*Pseudokirchneriella subcapitata* exposed to 150 mg/L for 24 h) (Vernouillet et al., 2010).
Venerupis decussata	96 h	Significant increase in total protein content (PROT), activity of superoxide dismutase (SOD), and a significant decrease in activity of catalase after exposure to 0.30, 3.00 and 9.00 µg/L (Almeida et al., 2017).
Vibrio fischeri	5 min/15 min	Significant inhibition of bacterial bioluminescence after exposure to 0.20-18 µg/L (Aguirre-Martinez et al., 2015).

2.3.4.2 Erythromycin

Twelve aquatic organisms were reported to exhibit sublethal effects of erythromycin at concentrations ranging from 0.05 µg/L to 100 mg/L and exposure times from 30 min to 28 d (Table 2.7). The lowest reported exposure time showing sublethal effects of erythromycin was 30 min for ultrasensitive *Escherichia coli*, exhibiting inhibition of initial adhesion of pure cultures on uncoated polystyrene surface after exposure to low concentrations (i.e., 0.5 and 50 µg/L) (Schreiber & Szewzy, 2008). Other reported aquatic organisms sensitive to erythromycin were *Carassius carassius*, *Chlorella vulgaris*, *Oncorhynchus mykiss*, and *Tetrahymena pyriformis*. Among them, *Tetrahymena pyriformis* was highly sensitive, exhibiting significant cell proliferation at ultra-low concentrations (i.e., 0.07 µg/L) after exposure for 24 h (Lang & Kohidai, 2012). An organism reported as expressing relatively low sensitivity to erythromycin was *Mytilus edulis,* exhibiting a significant decrease in phagocytosis and DNA damage on exposure (21 h) to high concentrations (i.e., 20 mg/L) (Lacaze et al., 2015). Thus, diverse aquatic organisms exhibited a variety of sublethal effects of erythromycin after exposure to a range of concentrations and exposure times.

Table 2.7. Sublethal effects of erythromycin.

Names of aquatic organisms	Exposure times (min/h/d)	Sublethal effects of erythromycin on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Aquabacterium commune	30 min	Inhibition of initial adhesion of pure cultures on uncoated polystyrene surface after exposure to 50 µg/L (Schreiber & Szewzyk, 2008).
Bacillus subtilis	30 min	Inhibition of initial adhesion of pure cultures on uncoated polystyrene surface after exposure to 50 µg/L (Schreiber & Szewzyk, 2008).
Carassius carassius	7 d/14 d	Significant decrease in activity of acetylcholinesterase (AChE) in brain after exposure to 2 µg/L (Liu et al., 2017).
Carassius auratus	28 d	Significant decrease in activity of acetylcholinesterase (AChE) in brain and increase in activity of superoxidase dismutase (SOD) and ethoxyresorufin-O-deethylase (EROD) in liver after exposure to 3.5, 18.8 and 70.5 µg/L (Liu et al., 2014).

Chlorella vulgaris	96 h	Significant increase in activity of superoxide dismutase (SOD), catalase (CAT), peroxidase (POD), and levels of malondialdehyde (MDA) and glutathione (GSH) contents after exposure to 20 µg/L (Wang et al., 2019).
Escherichia coli	30 min	Inhibition of initial adhesion of pure cultures on uncoated polystyrene surface after exposure to 0.5 and 50 µg/L (Schreiber & Szewzyk, 2008).
Mytilus edulis	21 h	Significant decrease in phagocytosis after exposure to 20 mg/L and 100 mg/L and significant DNA damage after exposure to 100 mg/L (Lacaze et al., 2015).
Oncorhynchus mykiss	96 h	Significant decrease in activity of catalase (CAT) after exposure to 0.1 mg/L and an increase in activity of glutathione reductase (GR) in gills after exposure to 1 mg/L. Significant increase in lipid peroxidation in gills after exposure to 0.010 mg/L and decrease in liver after exposure to 0.01, 0.1, 1 and 10 mg/L (Rodrigues et al., 2016).
	28 d	Significant decrease in activity of catalase (CAT) after exposure to 0.05 µg/L and 0.8 µg/L and increase in activity of glutathione peroxidase (GPx) after exposure to 0.4 µg/L in gills. Significant increase in lipid peroxidation in gills after exposure to 0.1, 0.2, 0.3 and 0.4 µg/L and decrease in liver after exposure to 0.2 and 0.8 µg/L (Rodrigues et al., 2016).
Phoca vitulina	66 h	Significant inhibition of proliferation of peripheral blood mononuclear cells after exposure to a concentration ranging from 0.75–150 µg/L (Kleinert et al., 2018).
Pseudokirchneriella subcapitata	72 h	Increase in activity of esterase and significant reduction of chlorophyll a content after exposure to 200 µg/L. Hyperpolarization of the mitochondrial membrane after exposure to 38-200 µg/L. Significant increase of intracellular glutathione (GSH) content after exposure to 38 µg/L (Machado & Soares, 2019).
Selenastrum capricornutum	96 h	Significant inhibition of growth after exposure to 0.06 mg/L and a decrease in photosynthetic rate after exposure to 0.3 mg/L. Significant decrease in chlorophyll a content after exposure to concentration >0.18 mg/L (Liu et al., 2011).
Tetrahymena pyriformis	24 h	Significant cell proliferation after exposure to concentrations ranging from 0.07-7.3 µg/L. Exhibition of chemo attractive character after exposure to 7.3 µg/L (Lang & Kohidai, 2012).

2.3.4.3 Fluoxetine

Sublethal effects of fluoxetine on 10 aquatic organisms were reported at concentrations ranging from 0.01 µg/L to 43.30 mg/L and exposure times from 1.5 h to 50 d (Table 2.8). The lowest reported exposure time showing sublethal effects of fluoxetine was 1.5 h for ultrasensitive *Gammarus pulex*, exhibiting a significant reduction in swimming activity at ultra-low concentrations (i.e., 0.01 µg/L) (De Lange et al., 2006). Other reported aquatic organisms sensitive to fluoxetine were *Acutodesmus obliquus*, *Danio rerio*, *Nannochloropsis limnetica*, and *Pseudokirchneriella subcapitata*. An organism reported as expressing relatively low sensitivity to fluoxetine was *Oncorhynchus mykiss*, exhibiting inhibition of basal activity of ethoxyresorufin-O-deethylase (EROD) in hepatocytes after exposure (24 h) to high concentrations (i.e., 43.30 mg/L) (Laville et al., 2004). Thus, a variety of sublethal effects of fluoxetine were

observed in diverse aquatic organisms after exposure to a range of concentrations and exposure times.

Table 2.8. Sublethal effects of fluoxetine.

Names of aquatic organisms	Exposure times (h/d)	Sublethal effects of fluoxetine on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Acutodesmus obliquus	50 d	A decrease in cell numbers and an increase in photosynthetic yield after exposure to 0.36 µg/L (Grzesiuk et al., 2018).
Ceriodaphnia dubia	7 d	Fecundity was decreased after exposure to a concentration of 223 µg/L (Brooks et al., 2003).
Danio rerio	96 h	Significant effect on metabolism of alanine, aspartate, glutamate, phenylalanine, tyrosine, starch, and sucrose and biosynthesis of phenylalanine, tyrosine, and tryptophan after exposure to 0.02, 0.12, 70 and 700 µg/L (Mishra et al., 2017)
	120 h	Significant inhibition of total swimming time (TST) after exposure to 15 µg/L and a significant increase at highest tested concentration of 500 µg/L (De Farias et al., 2019).
		Significant reduction in body length of zebrafish larvae after exposure to 10 µg/L. Significant inhibition in expression of circadian rhythm-related genes (nr1d1 and per2) after embryonic exposure to 0.1, 1 and 10 µg/L (Wu et al., 2017).
Daphnia magna	ND	Significant increase in a total number of Daphnia offspring produced after chronic exposure to 0.36 µg/L (Flaherty & Dodson, 2005).
Gammarus pulex	1.5 h	Significant reduction in swimming activity after exposure to a concentration range of 0.01-0.10 µg/L (De Lange et al., 2006).
Lemna minor	21 d	Decrease in root length by 100% and asexual reproduction by budding by 50% after exposure to 99.91 µg/L (Amy-Sagers et al., 2017).
Nannochloropsis limnetica	50 d	Increase in carotenoid to chlorophyll ratios after exposure to 0.36 µg/L (Grzesiuk et al., 2018).
Oncorhynchus mykiss	24 h	Inhibition of basal activity of ethoxyresorufin-O-deethylase (EROD) in primary rainbow trout hepatocytes after exposure to concentration range of 0.34-43.30 mg/L (Laville et al., 2004).
	48 h	Acceleration in rate of oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and decrease in levels of lipid peroxidation in microsomal membranes of hepatocytes after exposure to 3.09 µg/L (Gagne et al., 2006).
Pseudokirchneriella subcapitata	120 h	Significant reduction in growth (measured as turbidity) after exposure to 13.49 and 53.95 µg/L. Cell deformities were observed after exposure to 270 and 53.95 µg/L (Brooks et al., 2003).
Schmidtea mediterranea	9 d	Significant increase of 29.19% and 47.57% in locomotor activity and significant reduction of 19.91% and 28.57% in number of chironomid larvae consumed (feeding behaviour) after exposure to 1.0 and 10 µg/L, respectively. Significant reduction in fissioning (asexual reproduction) after exposure to 10 µg/L (Ofoegbu et al., 2019).

2.3.4.4 Metoprolol

Four aquatic organisms were reported to exhibit sublethal effects of metoprolol at concentrations ranging from 0.01 µg/L to 50 mg/L and exposure times from 12 h to 80 d (Table 2.9). The lowest reported exposure time showing sublethal effects of metoprolol was 12 h for *Cyprinus carpio*, exhibiting significant elevation of hydroperoxide content

(HPC) in liver and gills at ultra-low concentrations (i.e., 0.01 µg/L) (Martinez-Rodriguez et al., 2018). Another reported aquatic organism sensitive to metoprolol was *Oreochromis niloticus*, exhibiting significant increase in mRNA expression of vitellogenin related genes after exposure to low concentrations (i.e., 106.94 µg/L) (Groner et al., 2017). Organisms reported as expressing relatively low sensitivity to metoprolol were *Danio rerio* and *Hydra attenuata.* For example, *Danio rerio* exhibited scoliosis, retardation in growth, and abnormalities of heart in a 2-hour old embryo after exposure (72 h) to high concentrations (i.e., ≥25.3 mg/L) (Van den Brandhof & Montforts, 2010). Thus, diverse aquatic organisms exhibited a variety of sublethal effects of metoprolol after exposure to a range of concentrations and exposure times.

Table 2.9. Sublethal effects of metoprolol.

Names of aquatic organisms	Exposure times (h/d)	Sublethal effects of metoprolol on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Cyprinus carpio	12 h	Significant elevation of hydroperoxide content (HPC) in brain after exposure to 10 µg/L. Significant elevation of hydroperoxide content (HPC) in liver and gills after exposure to 0.01, 10 and 10000 µg/L (Martinez-Rodriguez et al., 2018).
	24 h	Significant elevation of hydroperoxide content (HPC) in brain after exposure to 10 and 10000 µg/L. Significant elevation of hydrogen peroxide content (HPC) in gills after exposure to 0.01 and 10 µg/L (Martinez-Rodriguez et al., 2018)
	48 h	Significant elevation of hydroperoxide content (HPC) in brain after exposure to 0.01, 10 and 10000 µg/L (Martinez-Rodriguez et al., 2018).
	72 h	Significant elevation of hydroperoxide content (HPC) in brain after exposure to 10 mg/L (Martinez-Rodriguez et al., 2018).
	96 h	Significant elevation of hydroperoxide content (HPC) in brain after exposure to 0.01 and 10 µg/L (Martinez-Rodriguez et al., 2018).
Danio rerio	72 h	Scoliosis in 2-hour old embryo at a concentration of 25.3 mg/L and retardation in growth and abnormalities of heart at concentrations higher than 25.3 mg/L (Van den Brandhof & Montforts, 2010).
Hydra attenuata	96 h	Significant reduction in morphology and feeding behaviour after exposure to 50 mg/L (Quinn et al., 2008).
Oreochromis niloticus	80 d	Significant increase in mRNA expression of vitellogenin related genes by 2.9-fold after exposure to 106.94 µg/L (Groner et al., 2017).

2.3.4.5 Naproxen

Sublethal effects of naproxen on five aquatic organisms were reported at concentrations ranging from 2.30 x 10^{-5} µg/L to 100 mg/L and exposure times from 24 h

to 32 d (Table 2.10). The lowest reported exposure time showing sublethal effects of naproxen was 24 h for *Tetrahymena pyriformis*, exhibiting significant chemoattractant effects at ultra-low concentrations (i.e., 2.30 x 10^{-5} µg/L) (Lang & Kohidai, 2012). Other reported aquatic organisms sensitive to naproxen were *Cyprinus carpio*, *Orconectes virilis*, and *Phoca vitulina*. For example, *Cyprinus carpio* exhibited significant developmental retardation in larvae after exposure to low concentrations (i.e., 0.01 mg/L) (Sehonova et al., 2017). Thus, a variety of sublethal effects of naproxen were observed in diverse aquatic organisms after exposure to a range of concentrations and exposure times.

Table 2.10. Sublethal effects of naproxen.

Names of aquatic organisms	Exposure times (h/d)	Sublethal effects of naproxen on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Cyprinus carpio	32 d	Significant developmental retardation in larvae after exposure to 0.01, 0.05, 0.10 and 0.20 mg/L (Sehonova et al., 2017).
	48 h	A decrease in reproduction and the no observed effect concentration (NOECs) for reproduction was 10 mg/L (Kwak et al., 2018).
Moina macrocopa	48 h	A decrease in reproduction and the no observed effect concentrations (NOECs) for reproduction was 0.3 mg/L (Kwak et al., 2018).
Orconectes virilis	23 h	Significant decrease in aggressive behaviour after exposure to 14 µg/L (Neal & Moore, 2017).
Phoca vitulina	66 h	Significant suppression of immune responses through inhibition of proliferation of peripheral blood mononuclear cells after exposure to a concentration ranging from 0.50-100 mg/L (Kleinert et al., 2018).
Tetrahymena pyriformis	24 h	Significant chemoattractant effect after exposure to 2.30 x 10^{-5} µg/L (Lang & Kohidai, 2012).

2.3.4.6 Ofloxacin

There was only one reported example of aquatic toxicity of ofloxacin (Table 2.11). A single species was tested at one exposure time (24 h) and three concentrations ranging from 0.1 mg/L to 100 mg/L. *Microcystis aeruginosa* showed sensitivity to ofloxacin, exhibiting an increase in chlorophyll a and carotenoids contents after exposure to low concentrations (i.e., 0.1 mg/L) (Deng et al., 2015).

Table 2.11. Sublethal effects of ofloxacin.

Names of aquatic organisms	Exposure time (h)	Sublethal effects of ofloxacin on aquatic organisms after exposure to a range of concentrations (mg/L)
Microcystis aeruginosa	24 h	Increase of chlorophyll a and carotenoids contents by 23% and 21%, respectively after exposure to 0.1 mg/L. Reduction in chlorophyll a and carotenoids contents by 42% and 35%, respectively after exposure to 10 mg/L. Significant inhibition of maximal photosystem system II (PSII) photochemical efficiency after exposure to 50-100 mg/L (Deng et al., 2015).

2.3.4.7 Sertraline

Aquatic organisms reported to be sensitive to sertraline were *Artemia franciscana* and *Gambusia holbrooki* (Table 2.12). *Artemia franciscana* exhibited a decrease in swimming speed after exposure (6 h) to low concentrations (i.e., 0.5 mg/L) (Morgana et al., 2018). *Gambusia holbrooki* exhibited a significant decrease in locomotor activity after exposure (144 h) to low concentrations (i.e., 10 µg/L) (Melvin, 2017).

Table 2.12. Sublethal effects of sertraline.

Names of aquatic organisms	Exposure times (h)	Sublethal effects of sertraline on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Artemia franciscana	6 h	A decrease in swimming speed began at 0.5 mg/L and significant inhibition of swimming activity after exposure to 7.26 mg/L (Morgana et al., 2018).
Gambusia holbrooki	144 h	Significant decrease in time spent on locomotor activity after exposure to 10 µg/L (Melvin, 2017).

2.3.4.8 Sulfamethoxazole

Six aquatic organisms were reported to exhibit sublethal effects of sulfamethoxazole at concentrations ranging from 0.003 µg/L to 50 mg/L and exposure times from 12 h to 21 d (Table 2.13). The lowest reported exposure time showing sublethal effects of sulfamethoxazole was 12 h for *Brachionus koreanus*, exhibiting a significant decrease in relative mRNA expression after exposure to 1 mg/L (Rhee et al., 2013). Other reported aquatic organisms sensitive to sulfamethoxazole were *Danio rerio* and *Tetrahymena pyriformis*. Among them, *Tetrahymena pyriformis* was highly sensitive, exhibiting chemoattractive character at ultra-low concentrations (i.e., 0.003 µg/L) after

exposure for 24 h (Lang & Kohidai, 2012). Organism reported as expressing relatively low sensitivity to sulfamethoxazole was *Procambarus clarkii*, exhibiting induction in transcriptional expression levels of glutathione S-transferase (GST) genes up to 5.7-fold and 3.6-fold in hemocytes and gills, respectively after exposure (72 h) to high concentrations (i.e., 50 mg/L) (Nicosia et al., 2014). Thus, diverse aquatic organisms exhibited a variety of sublethal effects of sulfamethoxazole after exposure to a range of concentrations and exposure times.

Table 2.13. Sublethal effects of sulfamethoxazole.

Names of aquatic organisms	Exposure times (h/d)	Sublethal effects of sulfamethoxazole on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Brachionus koreanus	12 h	Significant decrease in relative mRNA expression after exposure to 1 mg/L (Rhee et al., 2013).
	24 h	Significant decrease in relative mRNA expression after exposure to 0.1 and 1 mg/L. Significant decrease in activity of acetylcholinesterase (AChE) after exposure to 1 mg/L (Rhee et al., 2013).
Danio rerio	7 d	Significant decrease in spontaneous swimming activity (SSA) and a significant increase in heartbeat rate after exposure to 1µg/L, 10 µg/L, 100 µg/L, 1 mg/L and 10 mg/L. Induction in activity of glutathione S-transferase (GST) after exposure to 1 and 10 µg/L. Increase in production of malondialdehyde (MDA) production after exposure to a concentration ranging from 1-10 mg/L (Lin et al., 2014).
	21 d	Decrease in spermatozoa by 39.37±5.15% and increase in spermatocyte by 40.84±1.66% in males after exposure to 0.53 mg/L (Madureira et al., 2011).
Oncorhynchus mykiss	24 h	Inhibition of basal activity of ethoxyresorufin-O-deethylase (EROD) activity in primary rainbow trout hepatocytes after exposure to a concentration ranging from 0.99-126.63 mg/L (Laville et al., 2004).
	48 h	Acceleration in rate of oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and increase in levels of lipid peroxidation in microsomal membranes of hepatocytes after exposure to 25.3 mg/L (Gagne et al., 2006).
Procambarus clarkii	72 h	Transcriptional expression levels of glutathione S-transferase (GST) genes were significantly induced up to 5.7-fold and 3.6-fold in hemocytes and gills, respectively after exposure to 50 mg/L (Nicosia et al., 2014).
Selenastrum capricornutum	96 h	Significant inhibition of growth after exposure to 2.0 mg/L and a decrease in photosynthetic rate after exposure to 0.5 mg/L. Significant decrease in chlorophyll a content after exposure to 1.5 mg/L and carotenoids content after exposure to 1 mg/L (Liu et al., 2011).
Tetrahymena pyriformis	24 h	Exhibition of chemoattractive character after exposure to 0.003, 0.25 and 2533 µg/L (Lang & Kohidai, 2012).

2.3.4.9 Bisphenol A

Sublethal effects of bisphenol A on 19 aquatic organisms were reported at concentrations ranging from 0.001 µg/L to 160 mg/L and exposure times from 24 h to 180 d (Table 2.14). The lowest reported exposure time showing sublethal effects of

bisphenol A was 24 h for *Chironomus riparius*, exhibiting increase in activity of catalase (CAT) and glutathione S-transferase (GST) at ultra-low concentrations (i.e., 0.001 µg/L) (Lee & Choi, 2007). Other reported aquatic organisms sensitive to bisphenol A were *Dreissena polymorpha*, *Gobiocypris rarus, Haliotis diversicolor*, and *Physella acuta*. Organisms reported as expressing relatively low sensitivity to bisphenol A were *Eunapius fragilis, Hydra magnipapillata,* and *Monoraphidium braunii*. For example, *Eunapius fragilis* exhibited abnormal growth after exposure (6 d) to high concentrations (e.g., 16 mg/L) (Hill et al., 2002). Thus, a variety of sublethal effects of bisphenol A were observed in diverse aquatic organisms after exposure to a range of concentrations and exposure times.

Table 2.14. Sublethal effects of bisphenol A.

Names of aquatic organisms	Exposure times (h/d)	Sublethal effects of bisphenol A on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Carassius auratus	30 d	Significant reduction in ovary weight during exposure to 1, 50 and 500 µg/L, however weight recovered after exposure withdrawal. Significant reduction in testis weight during exposure to 50 and 500 µg/L, however weight not recovered after exposure withdrawal (Wang et al., 2019).
Chironomus riparius	24 h	Increase in activity of catalase (CAT) after exposure to 0.001 and 0.01 µg/L and glutathione S-transferase (GST) after exposure to 0.01, 1 and 10 µg/L. A decrease in activity of peroxidase (Px) after exposure to 0.1 and 10 µg/L (Lee & Choi, 2007).
	24 h/ 96 h	Significant DNA damage (measured by olive tail moments) after larval exposure to 0.5 mg/L and 3 mg/L (Martinez-Paz et al., 2013).
	48 h	Significant DNA damage (measured by the increase in the comet tail moments) after exposure to 1 mg/L (Lee et al., 2018).
Crassostrea angulata	16 d	Development of gonads are negatively affected in males, however accelerated in females after exposure to 2 mg/L (Luo et al., 2017).
Danio rerio	24 h	Loss of lateral line hair cells induced in a dose-dependent and time-dependent manner with concentrations of 0.23 mg/L or higher killing lateral line hair cells (Hayashi et al., 2015).
	48 h	Reduction in blood circulation, edema, malformation of the tail, and retardation in growth embryos exposed to a concentration of 8.5 mg/L (Schiller et al., 2013).
	72 h	Significant decrease in activity of acetylcholinesterase (AChE) after exposure to 0.78 µg/L for one day and 1 µg/L for two or three days (Chen et al., 2017).
	120 h	Increase in inflammation of swim bladder after exposure to 3.995 µg/L (Ortiz-Villanueva et al, 2018).
	21 d	Induction of synthesis of vitellogenin protein in liver after exposure to 1 mg/L (Van Den Belt et al., 2003).
	60 d	The ATP-coupled transmembrane transport of calcium and carbohydrate catabolism was affected in larval offspring from adults exposed to 20 µg/L (Chen et al., 2019b).

	75 d	Significant induction in synthesis of vitellogenin protein after exposure to concentration ≥375 µg/L. Significant reduction in juvenile growth, delay in spawning, alteration in mating behaviour, and reduction in egg number per female after exposure to concentration ≥1500 µg/L (Segner et al., 2003).
	150 d	Significant reductions in sperm motility, sperm ATP production, and a significant increase in sperm lipid peroxidation after continuous exposure to 0.29 µg/L for two generations. Reductions in hatching rates derived from maternal groups and significant adverse effects on malformations, including bent body, pericardial edema, and uninflated swim bladder (Chen et al., 2015).
	180 d	Reduction in length and weight in both males and females of F1 generation after exposure to 200 µg/L and F2 generation after exposure to 10, 200 and 400 µg/L at 90 days post fertilization (dpf). Reduction in length and weight was observed after exposure to the highest tested concentration of 400 µg/L at 180 dpf. Induction of synthesis of vitellogenin protein in males of F1 generation after exposure to 400 µg/L and F2 generation after exposure to 10 and 400 µg/L at 90 dpf (Keiter et al., 2012).
Daphnia magna	24 h	Stimulation of activity of catalase (CAT) after exposure to 5 mg/L (Kim et al., 2009).
		Inhibition of activity of catalase (CAT) after exposure to 30 µg/L (Park & Choi., 2009).
	48 h	Disorder of digestive, nervous, and antioxidative system leading to decrease in relative activities of trypsin, amylase (AMS), acetylcholinesterase (AChE), carbonic anhydrase (CA), glutathione peroxidase (GPx), and super oxidase dismutase (SOD) after exposure to 178 µg/L (Liu et al., 2019).
	21 d	Significant increase in dry weight after exposure to 2, 20, 200 and 2000 µg/L. Significant decrease in molting frequency after 20, 200 and 2000 µg/L (Li et al., 2018).
Dreissena polymorpha	14 d	Significant increase in activity of superoxidase dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) after exposure to 0.50 µg/L (Magini et al., 2017).
Eunapius fragilis	6 d	Abnormal growth was produced after exposure to 16 mg/L. New sponge growth spread into a thin sheet of cells. Germination was completely inhibited after exposure to 160 and 80 mg/L (Hill et al., 2002).
Gobiocypris rarus	7 d	Oxidative stress-induced due to a significant increase in production of hydrogen peroxide by 1.18, 1.23 and 1.34-fold in a concentration-dependent manner after exposure to 1, 225 and 1000 µg/L, respectively. Significant increase in nitric oxide (NO) content by 1.35-fold after exposure to 225 µg/L and significantly decreased by 1.41-fold after exposure to 1000 µg/L. Significant up-regulation of expressions of mRNA for iNOS (NO related genes) by 3.28-fold after exposure to 225 µg/L (Tao et al., 2016).
	21 d	Increase in malformation in development of embryo including bent spine and tail, delayed craniofacial cartilage ossification of larvae, and significant down regulation of transcripts of ossification related genes in offspring after maternal (adult females) exposure to 15 and 225 µg/L (Fan et al., 2018).
	28 d	Significant enhancement in activity of acetyl-CoA carboxylase (ACC) in both females and males by 1.32- and 1.22-fold, respectively. Significant increase in activity of fatty acid synthase (FASN) in both males and females by 1.27- fold and 1.32-fold, respectively. Activity of carnitine palmitoyl transferase (CPT1) was significantly decreased in females by 1.59-fold and significantly increased by 2.33-fold in males. Activity of glycerol-3-phosphate acyltransferase (GPAT) was significantly increased by 1.37-fold in males, while it did not affect its activity in females. The tested concentration of exposure was 15 µg/L (Guan et al., 2016).
Haliotis diversicolor	144 d	Increase in activity of Ca^{2+}–Mg^{2+}-ATPase by 40% after exposure to 100 µg/L (Zhou et al., 2010).
Heteromyenia sp.	6 d	Abnormal growth was produced after exposure to 16 ppm. Germination was initiated, but a tight cluster (or tube) of cells was produced that seemed to be exuded from the gemmule. Tissue lacked any organization, including water vascular system. Germination was completely inhibited after exposure to 80 and 160 mg/L (Hill et al., 2002).
Hydra magnipapillata	48 h	Retardation of head regeneration post-amputation after exposure to 3.424 mg/L, however only tentacles emerged post amputation after exposure to 1.141 mg/L (Murugadas et al., 2019).
	72 h	Only a few polyps were able to regenerate after exposure to 3.424 mg/L (Murugadas et al., 2019).
Lemna gibba	7 d	Significant reduction in frond density and growth rate after exposure to 20 and 54 mg/L (Mihaich et al., 2009).
Marisa cornuarietis	24 h	Lethargy, an abnormal extension of the mantle, lying on their sides and foot out of the shell with the little movement were observed in all treatment levels ≥6.84 mg/L at 25°C and ≥4.03 at 22°C (Mihaich et al., 2009).
Monoraphidium braunii	2 d	Significant decrease in cell number after exposure to 4 and 10 mg/L (Gattullo et al., 2012).

Oryzias latipes	60 d	Reduction in activity of catalase (CAT) in ovary. Significant increase in activity of superoxide dismutase (SOD) in intestine approximately by 82%. Stimulation in activity of glutathione S-transferase (GST) by approximately 57% in liver and 29% in gills. The levels of malondialdehyde (MDA) (biomarker for lipid peroxidation) were increased by approximately 41%, 72%, 140%, 157% and 87% in the liver, gill, intestine, testis, and ovary, respectively. The activity of acetylcholinesterase (AChE) was reduced by approximately 23%. The tested concentration was 1.5 mg/L (Li et al., 2016a).
	90 d	Induced testis–ova (intersex condition) after exposure to 10 µg/L (Metcalfe et al., 2001).
Physella acuta	48 h	Significant increase in activity of glutathione S-transferase (GST) after exposure to 500 µg/L (Morales et al., 2018).
Pimephales promelas	35 d	Significant increase in concentration of vitellogenin protein in plasma on sub-sampling days 7 and 14 after exposure to 15 µg/L (Schoenfuss et al., 2008).
Salmo trutta	96 d	Reduction of sperm density, motility rate, and swimming velocity at beginning of spawning after exposure to 1.75 µg/L. Reduction in swimming velocity and sperm motility in the middle of spawning after exposure to 2.40 µg/L (Lahnsteiner et al., 2005).
Xiphophorus hellerii	3 d	Expression of mRNA vitellogenin after exposure to 2 mg/L (Kwak et al., 2001).

2.3.4.10 Linear alkylbenzene sulfonate

There was only one reported example of aquatic toxicity of linear alkylbenzene sulfonate (Table 2.15). In this study, a single species was tested for one exposure time and four concentrations, ranging from ≤5 mg/L to 30 mg/L. *Lemna minor* showed relatively low sensitivity to linear alkylbenzene sulfonate, exhibiting increase in chlorophyll a content after exposure (8 d) to high concentrations (i.e., ≤5 mg/L) (Wang et al., 2012).

Table 2.15. Sublethal effects of linear alkylbenzene sulfonate.

Names of aquatic organisms	Exposure time (d)	Sublethal effects of linear alkylbenzene sulfonate on aquatic organisms after exposure to a range of concentrations (mg/L)
Lemna minor	8 d	Increase in frond number after exposure to concentrations ≤10 mg/L and significant inhibition of frond number after exposure to 30 mg/L. Increase in chlorophyll a content after exposure to concentration ≤5 mg/L and significant inhibition of chlorophyll a content after exposure to concentrations ≥20 mg/L. Significant increase in activity of glutathione S-peroxidase (GSH) contents after exposure to intermediate concentrations of 10-20 mg/L (Wang et al., 2012).

2.3.4.11 Nonylphenol

Eighteen aquatic organisms were reported to exhibit sublethal effects of nonylphenol at concentrations ranging from 0.5 µg/L to 5 mg/L and exposure times from 15 min to 112 d (Table 2.16). The lowest reported exposure time showing sublethal effects of nonylphenol was 15 min for *Microcystis aeruginosa*, exhibiting at least 10%

decrease in Photosystem II energy fluxes of non-toxic strain (CPCC632) after exposure to concentrations ranging from 0.25 to 5 mg/L (Perron & Juneau, 2011). Other reported aquatic organisms sensitive to nonylphenol were *Chironomus riparius*, *Corophium volutator*, *Crassostrea gigas*, *Cyprinus carpio,* and *Oncorhynchus mykiss*. Among them, *Oncorhynchus mykiss* was the most sensitive, exhibiting elevation in levels of vitellogenin protein in plasma of male rainbow trout after exposure (21 d) to low concentrations (i.e., 0.5 µg/L) (Jobling et al., 1996). Organisms reported as expressing relatively low sensitivity to nonylphenol were *Eunapius fragilis* and *Penicillium expansum*. For example, *Eunapius fragilis* exhibited abnormal growth with lack in tissue organization after exposure (6 d) to high concentrations (i.e., 2.2 mg/L) (Hill et al., 2002). Thus, diverse aquatic organisms exhibited a variety of sublethal effects of nonylphenol after exposure to a range of concentrations and exposure times.

Table 2.16. Sublethal effects of nonylphenol.

Names of aquatic organisms	Exposure times (min/h/d)	Sublethal effects of nonylphenol on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Bombina orientalis	10 d	Bent trunk, short tail, eye dysplasia, and cephalic dysplasia with ventral blister were observed in embryo after exposure to 0.22 mg/L (Park et al., 2010).
Chlorella sorokiniana	48 h	Significant increase in content of superoxide anion after exposure to 0.25 mg/L. Significant increase in activity of superoxide dismutase (SOD) and catalase (CAT) after exposure to 0.25 and 0.3 mg/L (Wang et al., 2018).
	96 h	Strong inhibition of algal cell growth after exposure to 0.30 mg/L (Wang et al., 2018).
Chironomus riparius	24 h/ 96 h	Significant DNA damage (measured by olive tail moments) after larval exposure to 1, 10 and 100 µg/L (Martinez-Paz et al., 2013).
Corophium volutator	80 d	Reduction in number with significant mortality at lowest (10 µg/L) and highest (200 µg/L) concentration of exposure. Reduction in mean length after exposure to 10, 50, 100 and 200 µg/L (Brown et al., 1999).
	100 d	The organisms were reduced by 50, 10.9, 17.4 and 78.3%, after exposure to 10, 50, 100 and 200 µg/L, respectively. Reduction in mean length after exposure to 10, 50, 100 and 200 µg/L (Brown et al., 1999).
Crassostrea gigas	72 h	Sperm motility is reduced to 12.5% after exposure to 100 µg/L and 30% after exposure to 1 µg/L (Nice, 2005).
Cyclotella caspia	96 h	Stimulation of algal growth after exposure to a concentration ≤0.18 mg/L and inhibition of algal growth after exposure to a concentration ≥0.18 mg/L. Toxic effects on algal morphology, including pigment fading, volume enlargement, increased cytoplasmic inclusion content, aggregation in two ends of cell, and cell rupture. Increase in activity of superoxide dismutase (SOD) after exposure to 0.22 and 0.26 mg/L (Liu et al., 2013).
Cyprinus carpio	70 d	Significant elevation of mean corpuscular volume (MVC), mean corpuscular hemoglobin (MCH), and total number of leukocytes after exposure to 15 µg/L (Schwaiger et al., 2000).

Danio rerio	60 d	Significant reduction in locomotor activity, aggressive behaviour, and group preference in male fish after exposure to 10 µg/L (Xia et al., 2010).
Dreissena polymorpha	48 h	Significant reduction in zebra mussel attachment and siphon extension after exposure to 5 and 10 mg/L (Quinn et al., 2006).
	112 d	Significant increase in alkali-labile phosphate (ALP) protein production in female mussel after prolonged exposure to 5 and 500 µg/L (Quinn et al., 2006).
Eunapius fragilis	6 d	Abnormal growth was produced after exposure to 22, 11 and 2.2 mg/L. Germination was initiated, but a tight cluster (or tube) of cells was produced that seemed to be exuded from gemmule. Tissue lacked any of the organization, including the water vascular system (Hill et al., 2002).
Heteromyenia sp.	6 d	Abnormal growth is produced after exposure to 22 and 11 mg/L. Germination was initiated, but a tight cluster (or tube) of cells was produced that seemed to be exuded from the gemmule. Tissue lacked any of the organization, including the water vascular system (Hill et al., 2002).
Lissotriton italicus	96 h	Abnormalities in mitochondria of endothelial and myocardial cells in cardiac muscle after exposure to 100 µg/L. Abnormalities included mitochondrial swelling, severe disruption or loss of cristae, and dilution of the matrix (Perrotta & Tripepi, 2012).
		Histological and ultrastructural changes in liver parenchyma, increase of intercellular spaces and melano-macrophagic component, more pronounced rough endoplasmic reticulum alterations and numerous large kupffer cells localized near the sinusoids, and numerous large lipid droplets aggregated in cluster and surrounded by glycogen granules after exposure to 50 and 100µg/L (Bernabo et al., 2014).
Microcystis aeruginosa	15 min	Photosystem II energy fluxes of non-toxic strain (CPCC632) were decreased at least by 10% after exposure to concentrations ranging from 0.25 to 5 mg/L (Perron & Juneau, 2011).
Oncorhynchus mykiss	48 h	Acceleration in rate of oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and increase in levels of lipid peroxidation in microsomal membranes of hepatocytes after exposure to 2.20 µg/L (Gagne et al., 2006).
	4 d	Significant elevation of liver somatic index (LSI) after exposure to 18 µg/L (Shelley et al., 2012)
	21 d	Elevation in plasma level of vitellogenin protein in male rainbow trout, resulting in concomitant inhibition of testicular growth. The tested concentrations were 0.5, 1.32, 3.5, 9.3, 24 and 65 µg/L (Jobling et al., 1996).
Oryzias latipes	104 d	Reduction in survival of embryo and development of sex characteristics after embryonic exposure within 24-h post fertilization (hpf). The no observed effect concentration (NOEC) was 8.2 µg/L and the lowest observed effect concentration (LOEC) was 17.7 µg/L (Yokota et al., 2001).
Penicillium expansum	48 h	Significant increase in activity of superoxide dismutase (SOD) by 4-fold and catalase (CAT) by 1.3-fold after exposure to 100 mg/L (Kuzikova et al., 2017).
Planktothrix agardhii	4 d	Significant increase in activity of superoxide dismutase (SOD) with 2.7-fold, catalase (CAT) with 3.9-fold, and glutathione S-transferase (GST) with 3.6-fold after exposure to 2 mg/L. Significant increase in levels of malonaldehyde (MDH) up to 300% after exposure to 2 mg/L (Medvedeva et al., 2017).
Poecilia reticulata	4 d	Significant decrease in activity of acetylcholine esterase (AChE) in muscle tissue after exposure to 150 and 300 µg/L (Li, 2008).
	7 d	Decrease of 30- 40% in activity of acetylcholine esterase (AChE) in muscle after exposure to 60 and 150 µg/L. Increase of 40% in activity of carboxylesterase (CbE) in liver after exposure to 10, 60 and 150 µg/L (Li, 2008).

2.3.4.12 Triclosan

Sublethal effects of triclosan on 17 aquatic organisms were reported at concentrations ranging from 0.1 µg/L to 2.5 mg/L and exposure times from 20 min to 45 d (Table 2.17). The lowest reported exposure time showing sublethal effects of triclosan was 20 min for *Strongylocentrotus nudus*, exhibiting a decrease in fertilization rate by

97.4%, 92.9% and 82.7% after exposure to 0.03, 0.14 and 0.29 mg/L, respectively (Hwang et al., 2014). Other reported aquatic organisms sensitive to triclosan were *Dreissena polymorpha*, *Microcystis aeruginosa*, and *Oncorhynchus mykiss.* For example, *Dreissena polymorpha* exhibited a significant increase in activity of glutathione S-transferase (GST) enzyme after exposure (24 h) to low concentrations (i.e., 0.29 µg/L) (Parolini et al., 2013). An organism reported as expressing relatively low sensitivity to triclosan was *Pelophylax perezi*, exhibiting a significant delay in hatching rate after exposure (72 h) to high concentrations (i.e., 1.4 mg/L) (Martins et al., 2017). Thus, a variety of sublethal effects of triclosan were observed in diverse aquatic organisms after exposure to a range of concentrations and exposure times.

Table 2.17. Sublethal effects of triclosan.

Names of aquatic organisms	Exposure times (h/d)	Sublethal effects of triclosan on aquatic organisms after exposure to a range of concentrations (mg/L and µg/L)
Brachionus calyciflorus	4 d	Increase in hatching rate from 0.402 to 0.502 and 0.475, respectively after exposure of resting eggs to 0.1 and 1.0 µg/L. Significant decrease in hatching rate from 0.402 to 0.34, when the resting eggs were formed in the control medium and hatched in medium with triclosan at a concentration of 200 µg/L (Zhang et al., 2016).
Caenorhabditis elegans	24 h	Significant increase in germline toxicity after exposure to 1 mg/L. A significant delay in hatching after exposure to a concentrations ranging from 0.1-2 mg/L in a concentration-dependent manner (Lenz et al., 2017).
Chlamydomonas reinhardtii	96 h	Significant decrease in growth and chlorophyll content and a significant increase in levels of lipid peroxidation after exposure to 405.3 µg/L. Significant increase in transcription of superoxidase mutase (SOD) enzyme related genes after exposure to 88.9 and 405.3 µg/L (Pan et al., 2018).
Chironomus riparius	24 h/ 96 h	Significant DNA damage (measured by olive tail moments) after larval exposure to 10, 100 and 1000 µg/L (Martinez-Paz et al., 2013).
Cymbella sp	72 h	Scanning electron microscope images (SEM) reflect that diatoms cells were enormously damaged after exposure to 1 mg/L (Ding et al., 2018).
Danio rerio	24 h	Significant induction in activity of glutathione peroxidase (GPx) and catalase (CAT) after exposure to 1 µg/L (Parenti et al., 2019).
	48 h	Absence of pigmentation, missing eye primordial, underdeveloped tail, and malformation in cardiovascular system after exposure to 1.25 mg/L. Specific cardiovascular disorders, such as pericardial edema and slow heart beats in 60% of the embryos after exposure to 1.25 mg/L and 30% of the embryos after exposure to 0.625 mg/L (Zhu et al., 2018).
		Significant reduction of hatching rates in embryos after exposure to 1 mg/L at 72-hour post fertilization (hpf) (Zhou et al., 2019a).
	120 h	Significant reduction in activity of superoxide dismutase (SOD) after exposure to 0.1 µg/L. Significant induction in activity of catalase (CAT) after exposure to 0.1 and 1 µg/L, and of glutathione peroxidase (GPx) after exposure to 1 µg/L (Parenti et al., 2019).

	6 d	Significant increase in activity of acetylcholinesterase (AChE) and lactate dehydrogenase (LDH) after larval exposure to 0.25 mg/L and glutathione S-transferase (GST) after larval exposure to 0.25 and 0.35 mg/L (Oliveira et al., 2009).
	7 d	Significant increase in hatching rate after 72 h exposure to 2, 20 and 100 µg/L. Significant delay in hatching for embryos exposed to 50 µg/L. Significant increase in activity of acetylcholinesterase (AChE) activity and glutathione peroxidase (GPx) in embryos exposed to 50 µg/L and 100 µg/L (Falisse et al., 2017).
Daphnia magna	48 h	General oxidative stress condition leading to an elevation in amino acid concentrations, particularly valine, isoleucine, glutamate, glutamine, and methionine after exposure to a sublethal concentration range of 6.25–100 µg/L (Kovacevic et al., 2016).
Daphnia pulex	ND	Significant inhibition of Dappu HR96, a nuclear receptor after exposure to 28.95 µg/L (Karimullina et al., 2012)
Dreissena polymorpha	24 h	Significant increase in activity of glutathione S-transferase (GST) after exposure to 0.29 µg/L (Parolini et al., 2013).
	48 h	Significant increase in activity of glutathione peroxidase (GPx) and glutathione S-transferase (GST) after exposure to 0.29 µg/L (Parolini et al., 2013).
	72 h	Significant increase in activity of catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST) after exposure to 0.29 µg/L (Parolini et al., 2013).
	96 h	Significant increase in activity of glutathione peroxidase (GPx) and glutathione S-transferase (GST) after exposure to 0.29 µg/L (Parolini et al., 2013).
	7 d	Significant alterations in protein expression profiles in gills, with eleven protein spots upregulated while only one single protein spot depressed. This effects various biological processes, especially those involved in calcium-binding or stress response. The exposure concentration was 0.58 µg/L (Riva et al., 2012).
Microcystis aeruginosa	96 h	Significant increase in activity of superoxide dismutase (SOD) after exposure to 0.25 µg/L and significantly decreased, after exposure to 2 µg/L. Significant increase in activity of glutathione S-transferase (GSH) after exposure to 0.1, 0.25, 0.5, 1 and 2 µg/L (Huang et al., 2016).
Oncorhynchus mykiss	40 d	Histopathological effects were observed including lamellar fusion, hyperplasia, epithelial necrosis, hypertrophy, and epithelial lifting in gill. Melanomacrophage centers in spleen, necrotic hepatocytes in liver, and cloudy swelling in tubules and glomerular capillaries dilation in kidneys were observed. The tested concentration was 0.48 ± 0.2 µg/L (Capkin et al., 2017).
Oryzias latipes	9 d	Significant decrease in swimming speed on day 6 and 8 after exposure to 0.17 mg/L (Nassef et al., 2010).
	61 d	Alteration on fish behavior and erratic swimming after exposure to 71 µg/L (Orvos et al., 2002).
Pangasianodon hypophthalmus	45 d	Significant decrease in total erythrocyte count (TEC), hemoglobin (Hb) content and packed cell volume, however there was an increase in total leukocyte count. Significant increase in activity of catalase (CAT), superoxide dismutase (SOD), and glutathione-S-transferase (GST) in both gill and liver tissue. Significant decrease in activity of acetylcholinesterase (AChE) in brain. All three sublethal effects were produced after exposure to 97, 145 and 291 µg/L (Sahu et al., 2018).
Pelophylax perezi	72 h	Significant delay in hatching rate after exposure to 1.4 and 2.5 mg/L (Martins et al., 2017).
	120 h	Delay in development of eye in larvae, which did not present transparent cornea after exposure to 1.4 mg/L (Martins et al., 2017).
	144 h	Significant delay in development of larvae after exposure to 2.5 mg/L (Martins et al., 2017).
Strongylocentrotus nudus	20 min	Sperm viability was decreased by 13% and 22% after exposure to 0.29 and 0.43 mg/L, respectively. Decrease in fertilization rate by 97.4%, 92.9 % and 82.7% after exposure to 0.03, 0.14 and 0.29 mg/L, respectively (Hwang et al., 2014).
Tetrahymena thermophila	1 h	Significant DNA damage after exposure to 1 µg/L (Gao et al., 2015)

Xiphophorus hellerii	24 h/72 h/ 168 h	In females, mRNA expression of CYP1A gene was inhibited at the lowest tested dose of 0.002 mg/L and significantly induced at highest tested dose of 1.25 mg/L. In males, mRNA expression levels of the CYP1A gene rapidly increase at the middle (0.25 mg/L) and highest (1.25 mg/L) tested dose, and exhibited a good time-dependent increase at lowest tested dose of 0.002 mg/L. Activity of ethoxyresorufin O-deethylase (EROD) was just induced at highest tested dose of 1.25 mg/L after 24 h exposure and middle tested dose of 0.25 mg/L after 72 h exposure for females. In males, EROD activities are time-dependent and reached the maximum at lowest tested dose of 0.002 mg/L after 168 h exposure, but at middle and highest tested doses reached the maximum level after 24-h exposure (Liang et al., 2013).

2.3.5 Summary assessment of sublethal effects of PPCPs on aquatic organisms

This review revealed that a wide diversity of aquatic organisms (n=79) were affected by exposure to PPCPs, consistent with the findings of Daughton and Ternes (1999) and Boxall (2004), even at ultra-low concentrations, as noted by De Lange et al. (2006), Lang and Kohidai (2012), and Martinez-Rodriguez et al. (2018). Multiple types of PPCPs are present in water bodies at different concentrations (Ros et al., 2018), which can affect the organisms in their natural environments. These effects include behavioral alterations, histological changes, biochemical responses, genotoxicity, and/or cytotoxicity, occurring after exposure to PPCPs (Boxall et al., 2012).

Sublethal effects were consistently reported in diverse aquatic organisms after chronic exposure to environmentally relevant low concentrations of PPCPs (Martinez Gomez, Baca & Walsh, 2015; Rodea-Palomares et al., 2016). For example, there was a significant reduction in swimming activity in a crustacean (*Gammarus pulex*) at ultra-low concentrations (i.e., 0.01 μg/L) of carbamazepine (De Lange et al., 2006). An increase in activity of antioxidant enzymes and levels of lipid peroxidation were observed in a mollusc (*Mytilus galloprovincialis*) after exposure to 10 μg/L of carbamazepine (Oliveira et al., 2017). In zebrafish (*Danio rerio*), there was a reduction in body length and significant inhibition in the expression of circadian rhythm-related genes after embryonic exposure to 10 μg/L of fluoxetine (Wu et al., 2017). In algae (*Pseudokirchneriella subcapitata*), a significant reduction of chlorophyll a content was observed after exposure

to 200 μg/L of erythromycin (Machado & Soares, 2019). An increase in activity of catalase (CAT) and glutathione S-transferase (GST) was observed in arthropod (*Chironomus riparius*) at ultra-low concentrations (i.e., 0.001 μg/L) of bisphenol A (Lee & Choi, 2007). Thus, the occurrence of PPCPs in the aquatic environment is affecting diverse organisms of aquatic biota, even when present at very low concentrations.

Some priority PPCPs were reported to produce sublethal effects in a relatively large number of aquatic organisms, such as carbamazepine (n=26), bisphenol A (n=19), nonylphenol (n=18), and triclosan (n=17) (Tables 2.6, 2.14, 2.16 and 2.17). Priority PPCPs reported to produce relatively stronger sublethal effects in aquatic organisms include carbamazepine, erythromycin, metoprolol, sulfamethoxazole, bisphenol A, nonylphenol, and triclosan (Tables 2.6, 2.7, 2.9, 2.13, 2.14, 2.16 and 2.17). These compounds cause a significant increase in activity of antioxidant enzymes, including catalase (CAT), glutathione S-transferase (GST), glutathione peroxidase (GPx), glutathione reductase (GR), and superoxidase dismutase (SOD) in tissues of gill, intestine, liver, and muscle in aquatic organisms (Kim et al., 2009; Li et al., 2009; Li et al., 2011; Zhang et al., 2012; Liu et al., 2013; Liu et al., 2014; Lin et al., 2014; Huang et al., 2016; Rodrigues et al., 2016; Almeida et al., 2017; Kuzikova et al., 2017; Magini et al., 2017; Morales et al., 2018; Pan et al., 2018; Wang et al., 2018; Liu et al., 2019; Parenti et al., 2019; Wang et al., 2019). These compounds also cause a significant increase in levels of lipid peroxidation, elevation of hydroperoxide content (HPC), and significant inhibition in activity of acetylcholinesterase (AChE) in tissues of different organs (Li, 2008; Oliveira et al., 2009; Rhee et al., 2013; Liu et al., 2014; Li et al., 2016a; Chen et al., 2017; Liu et al., 2017; Aguirre-Martinez et al., 2018; Martinez-Rodriguez et al., 2018; Sahu et al., 2018; Liu et al., 2019). Thus, the activation of antioxidant

machinery in aquatic organisms after exposure to PPCPs demonstrates their stronger sublethal effects.

Some aquatic organisms were reported to consistently exhibit sublethal effects after exposure to many priority PPCPs. For example, *Danio rerio* exhibited a variety of sublethal effects after exposure to carbamazepine, fluoxetine, metoprolol, sulfamethoxazole, bisphenol A, nonylphenol, and triclosan (Tables 2.6, 2.8, 2.9, 2.13, 2.14, 2.16 and 2.17). It exhibited a significant reduction in locomotor activity after exposure to fluoxetine, sulfamethoxazole, and nonylphenol (Xia et al., 2010; Lin et al., 2014; De Farias et al., 2019) and tail and heart deformities after exposure to carbamazepine and metoprolol (Van den Brandhof & Montforts, 2010). *Oncorhynchus mykiss* exhibited a variety of sublethal effects after exposure to carbamazepine, erythromycin, fluoxetine, sulfamethoxazole, nonylphenol, and triclosan (Tables 2.6, 2.7, 2.8, 2.13, 2.16 and 2.17). It exhibited an increase in activities of antioxidant enzymes including CAT, GPx, GR, and SOD after exposure to carbamazepine (Li et al., 2011) and GPx and GR enzymes after exposure to erythromycin (Rodrigues et al., 2016). It also exhibited acceleration in oxidation rate of reduced nicotinamide adenine dinucleotide phosphate (NADPH) after exposure to carbamazepine, fluoxetine, sulfamethoxazole, and nonylphenol (Gagne et al., 2006).

Priority PPCPs widely studied for their sublethal effects include carbamazepine, erythromycin, fluoxetine, metoprolol, naproxen, sulfamethoxazole, bisphenol A, nonylphenol, and triclosan (Tables 2.6, 2.7, 2.8, 2.9, 2.10, 2.13, 2.14, 2.16 and 2.17). These PPCPs produced a wide variety of sublethal effects including behavioural alterations, histological changes, and biochemical responses in diverse aquatic organisms. Priority PPCPs less frequently studied for their sublethal effects were ofloxacin,

sertraline, and linear alkylbenzene sulfonate (Tables 2.11, 2.12 and 2.15). There were few examples of sublethal effects identified for the infrequently studied PPCPs. Further, wide ranges of sublethal concentrations were reported for all the priority PPCPs, with a minimum of four orders of magnitude of difference between highest and lowest reported sublethal concentrations for triclosan only (i.e., 0.1 μg/L to 2.5 mg/L). Thus, there was a lack of consensus among the recorded thresholds of sublethal effects for priority PPCPs. There was no PPCP or organism for which there was more than one study reporting on the same sublethal effects for the same exposure parameters (time and concentrations) for the same PPCP and the same organism. Reported sublethal concentrations also vary due to different sensitivities in different aquatic organisms exposed.

2.3.6 Lethal effects of PPCPs on aquatic organisms

PPCPs in aquatic environments can affect aquatic organisms lethally by immobilizing, inhibiting growth, or completely killing the organisms (Martinez Gomez et al., 2015; Ros et al., 2018). As concentrations increase in aquatic environments, sublethal effects may aggregate and causes lethality in organisms (Ros et al., 2018). Lethal effects are investigated by identifying lethal concentrations including EC50, IC50, and LC50 for different aquatic organisms (Harada et al., 2008). The lethal effects are examined to fully explore the ecotoxicity of PPCPs, although environmentally relevant concentrations of PPCPs occur at lower than lethal levels (Straub, 2013). Lethal concentrations of PPCPs for different aquatic organisms (n=60) were identified from laboratory-based studies and presented for each of the twelve priority PPCPs (Tables 2.18-2.19).

Table 2.18. Lethal effects of priority pharmaceuticals, organized by compound, organism, and exposure time. Lethal concentrations selected for calculating SD indicated in grey. Concentrations are expressed in mg/L. ND=No Data.

Names of the aquatic organisms	Exposure times (min/h/d)	Acute median effective/inhibitory/lethal concentrations (E/I/LC50s)							
		Carbamazepine	Erythromycin	Fluoxetine	Metoprolol	Naproxen	Ofloxacin	Sertraline	Sulfamethoxazole
Artemia franciscana	24 h	ND	ND	ND	ND	ND	ND	9.58 (LC50) (Morgana et al., 2018)	ND
	6 h	ND	ND	ND	ND	ND	ND	7.26 (EC50) Alteration in swimming speed (Morgana et al., 2018)	ND
Brachionus calyciflorus	24 h	ND	27.53 (LC50) (Isidori et al., 2005a)	ND	ND	62.48 (LC50) (Isidori et al., 2005b)	ND	ND	26.27 (LC50) (Isidori et al., 2005a)
	48 h	ND	0.94 (EC50) (Isidori et al., 2005a)	ND	ND	ND	ND	ND	9.63 (EC50) (Isidori et al., 2005a)
Brachionus koreanus	24 h	138.6 (LC50) (Rhee et al., 2012)	ND	ND	ND	ND	ND	ND	ND
Ceriodaphnia dubia	24 h	ND	ND	ND	ND	ND	17.41 (LC50) (Isidori et al., 2005a)	ND	15.51 (LC50) (Isidori et al., 2005a)
	48 h	77.7 (EC50) (Ferrari et al., 2003)	10.23 (EC50) (Isidori et al., 2005a)	0.23 (LC50) (Brooks et al., 2003)	ND	66.4 (EC50) (Isidori et al., 2005b)	ND	ND	ND
Chlorella vulgaris	24 h	110.93 (EC50) (Jos et al., 2003)	ND	ND	ND	ND	ND	ND	ND
	48 h	36.62 (EC50) (Jos et al., 2003)	ND	ND	ND	ND	ND	ND	0.0062 (EC50) (Baran et al., 2006)

	96 h	ND	0.0857 (LC50) (Wang et al., 2019)	4.3 (IC50) (Johnson et al., 2007)	ND	ND	ND	0.76 (IC50) (Johnson et al., 2007)	ND
Chlorella pyrenoidosa	24 h	1339.43 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND
	48 h	239.84 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND
	72 h	167.33 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND
	96 h	49.40 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND
	144 h	33.11 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND
Cyprinus carpio	96 h	ND	ND	ND	ND	269.15 (LC50) (Gheorghe et al., 2016)	ND	ND	ND
Danio rerio	48 h	6.25 (LC50) (Zhou et al., 2019a)	ND	8.45 (EC50) (Hatching) (De Farias et al., 2019)	ND	ND	ND	ND	ND
		53.05 (LC50) (Shao et al., 2019)	ND	ND	ND	ND	ND	ND	ND
		46.53 (EC50) (Weichert et al., 2017)	ND	ND	ND	ND	ND	ND	ND
	72 h	86.50 (EC50) ≥245 (LC50) (Van den Brandhof & Montforts, 2010)	ND	ND	31.0 (EC50) 101 (LC50) (Van den Brandhof & Montforts, 2010)	ND	ND	ND	ND

		>118 (LC50) (Weigt et al., 2011)	ND	ND	ND	ND	ND	ND	ND
	96 h	ND	ND	ND	ND	98.3 (EC50) (Embryo) 149.0 (EC50) (Larvae) 115.2 (LC50) (Embryo) 147.6 (LC50) (Larvae) (Li et al., 2016b)	ND	ND	ND
Daphnia magna	24 h	112.23 (EC50) (Jos et al., 2003)	22.45 (EC50) (Isidori et al., 2005a)	ND	ND	ND	ND	3.1 (LC50) (Minagh et al., 2009)	25.2 (EC50) (Isidori et al., 2005a)
		ND	387.7 (EC50) (Di Delupis et al., 1992)	ND	ND	ND	ND	ND	ND
	48 h	>100 (LC50) (Cleuvers, 2003)	7.80 (EC50) (Sanderson et al., 2003)	27 (EC50) (pH 6.0) 4.6 (EC50) (pH 7.5) 0.75 (EC50) (pH 9.0) (Bostrom & Berglund, 2015)	438 (EC50) (Cleuvers, 2003)	10 (EC50) (pH 6.0) 25 (EC50) (pH 7.5) 96 (EC50) (pH 9.0) (Bostrom & Berglund, 2015)	ND	8.5 (EC50) (pH 6.0) 1.2 (EC50) (pH 7.5) 0.18 (EC50) (pH 9.0) (Bostrom & Berglund, 2015)	10 (LC50) (Cunningham et al., 2006)
		ND	207.8 (EC50) (Ji et al., 2012)	0.82 (LC50) (Brooks et al., 2003)	8.8 (LC50) (Cunningham et al., 2006)	46.72 (EC50) (Gheorghe et al., 2016)	ND	0.920 (EC50) (Christensen et al., 2006)	4.5 (EC50) (Sanderson et al., 2003)
		14.9 (LC50) (Duan et al., 2019)	210.57 (EC50) (Di Delupis et al., 1992)	438 (EC50) (Cleuvers, 2005)	ND	85.34 (EC50) (Kwak et al., 2018)	ND	1.3 (LC50) (Minagh et al., 2009)	75.3 (EC50) (Osorio et al., 2016)
		111 (LC50) (Han et al., 2006)	ND	0.51 (LC50) (Cunningham et al., 2006)	ND	166.3 (EC50) (Cleuvers, 2004)	ND	ND	123.1 (EC50) (Park & Choi, 2008)
		13.8 (EC50) (Ferrari et al., 2003)	ND	ND	ND	ND	ND	ND	189.2 (EC50) (Kim et al., 2007)

		97.82 (EC50) (Jos et al., 2003)	ND	ND	ND	ND	ND	ND	205.2 (EC50) (Jung et al., 2007)
		111.0 (EC50) (Sanderson et al., 2003)	ND	ND	ND	ND	ND	ND	ND
	96 h	76.3 (EC50) (Kim et al., 2007)	ND	ND	ND	ND	ND	ND	177.6 (EC50) (Jung et al., 2007)
		ND	ND	ND	ND	ND	ND	ND	177.3 (EC50) (Kim et al., 2007)
	21 d	ND	ND	ND	ND	ND	ND	0.066 (EC50) 0.12 (LC50) (Minagh et al., 2009)	ND
Dreissena polymorpha	96 h	5.09 (EC50) (Gill cells) 6.78 (EC50) (Digestive gland cells) 5.29 (EC50) (Haemocytes) (Parolini et al., 2011)	ND	ND	ND	ND	ND	ND	ND
Gammarus pulex	24 h	>112 (LC50) (Gomez-Canela et al., 2016)	ND	ND	ND	ND	ND	ND	102.79 (LC50) (Gomez-Canela et al., 2016)
Hydra attenuata	96 h	29.4 (LC50) 15.52 (EC50) (Morphology) 3.76 (EC50) (Feeding) (Quinn et al., 2008)	ND	ND	ND	22.36 (LC50) 2.62 (EC50) (Morphology) 2.68 (EC50) (Feeding) (Quinn et al., 2008)	ND	ND	ND
Hydra magnipapillata	24 h	8.66 (LC50) (Murugadas et al., 2019)	ND	ND	ND	51.99 (LC50) (Yamindago et al., 2019)	ND	ND	ND
	48 h	6.75 (LC50) (Murugadas et al., 2019)	ND	ND	ND	44.93 (LC50) (Yamindago et al., 2019)	ND	ND	ND

	72 h	5.34 (LC50) (Murugadas et al., 2019)	ND	ND	ND	42.50 (LC50) (Yamindago et al., 2019)	ND	ND	ND
	96 h	5.13 (LC50) (Murugadas et al., 2019)	ND	ND	ND	ND	ND	ND	ND
Lemna gibba	7 d	ND	ND	ND	ND	ND	ND	ND	0.081 (EC50) (Wet mass) 0.249 (EC50) (Frond number) 0.985 (EC50) (Chlorophyll-a) 0.682 (EC50) (Chlorophyll-b) 4.983 (EC50) (Carotenoids) (Brain et al., 2004)
Lemna minor	7 d	ND	ND	ND	320 (EC50) (Cleuvers, 2005)	ND	ND	ND	ND
Microcystis aeruginosa	24 h	ND	ND	ND	ND	ND	ND	ND	0.55 (EC50) (Van der Grinten et al., 2010)
Moina macrocopa	48 h	ND	135.5 (EC50) (Ji et al., 2012)	ND	ND	74.13 (EC50) (Kwak et al., 2018)	ND	ND	ND
Oncorhynchus mykiss	24 h	75.13 (EC50) (Laville et al., 2004)	ND	ND	ND	ND	ND	ND	27.35 (EC50) (Laville et al., 2004)
	96 h	19.9 (LC50) (Li et al., 2011)	ND	ND	ND	ND	ND	0.38 (LC50) (Minagh et al., 2009)	ND
Oryzias latipes	48 h	35.4 (LC50) (Kim et al., 2007)	ND	ND	31(LC50) (Van den Brandhof & Montforts, 2010)	ND	ND	ND	>750 (Kim et al., 2007)

	96 h	35.4 (LC50) (Kim et al., 2007)	ND	5.5 (LC50) (Nakamura et al., 2008)	ND	ND	ND	ND	562.5 (Kim et al., 2007)
Pimephales promelas	48 h	ND	ND	0.70 (LC50) (Brooks et al., 2003)	ND	ND	ND	0.072 (EC50) (Valenti et al., 2009)	ND
		ND	ND	0.19 (LC50) (Stanley et al., 2007)	ND	ND	ND	ND	ND
	96 h	101.0 (EC50) (Sanderson et al., 2003)	61.0 (EC50) (Sanderson et al., 2003)	ND	ND	ND	ND	ND	890.0 (EC50) (Sanderson et al., 2003)
Pseudokirchneriella subcapitata	48 h	48.9 (EC50) (Harada et al., 2008)	0.24 (EC50) (Christensen et al., 2006)	ND	ND	ND	ND	0.043 (EC50) (Christensen et al., 2006)	70 (EC50) (Sanderson et al., 2003)
		51 (EC50) (Sanderson et al., 2003)	4.3 (EC50) (Sanderson et al., 2003)	ND	ND	ND	ND	ND	ND
	72 h	ND	0.02 (EC50) (Isidori et al., 2005a)	0.202 (IC50) (Minguez et al., 2016)	>320 (EC50) (Cleuvers, 2003)	>80 (EC50) (González-Pleiter et al., 2013)	ND	0.150 (IC50) (Minguez et al., 2016)	0.52 (EC50) (Isidori et al., 2005a)
		ND	0.038 (EC50) (Machado & Soares, 2019)	ND	ND	ND	1.44 (EC50) (Isidori et al., 2005a)	0.14 (EC50) (Minagh et al., 2009)	1.9 (IC50) (Yang et al., 2008)
		ND	0.35 (EC50) (González-Pleiter et al., 2013)	ND	ND	ND	ND	ND	ND
	96 h	>500 (IC50) (Aguirre-Martinez et al., 2015)	ND	0.044 (IC50) (Johnson et al., 2007)	ND	ND	0.004 (EC50) (Ferrari et al., 2004)	0.012 (IC50) (Johnson et al., 2007)	0.146 (EC50) (Ferrari et al., 2004)
Scenedesmus acutus	96 h	ND	ND	0.091 (IC50) (Johnson et al., 2007)	ND	ND	ND	0.098 (IC50) (Johnson et al., 2007)	ND
Scenedesmus obliquus	24 h	200.82 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND

	48 h	72.97 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	0.11 (EC50) (Xiong et al., 2019)
	72 h	89.12 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND
	96 h	70.10 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND
	144 h	54.60 (EC50) (Zhang et al., 2012)	ND	ND	ND	ND	ND	ND	ND
Scenedesmus quadricauda	96 h	ND	ND	0.122 (IC50) (Johnson et al., 2007)	ND	ND	ND	0.317 (IC50) (Johnson et al., 2007)	ND
Schmidtea mediterranea	48 h	ND	ND	0.357 (LC50) (Ofoegbu et al., 2019)	ND	ND	ND	ND	ND
	96 h	ND	ND	0.16 (LC50) (Ofoegbu et al., 2019)	ND	ND	ND	ND	ND
Selenastrum capricornutum	72 h	ND	ND	ND	ND	ND	ND	ND	0.52 (EC50) (Isidori et al., 2005a)
Skeletonema marinoi	72 h	ND	ND	0.048 (IC50) (Minguez et al., 2018)	ND	ND	ND	0.016 (EC50) (Minguez et al., 2018)	ND
Thamnocephalus platyurus	24 h	140 (LC50) (Nałecz-Jawecki & Persoone, 2006)	17.68 (LC50) (Isidori et al., 2005a)	0.76 (LC50) (Nałecz-Jawecki, 2007)	ND	84.09 (LC50) (Isidori et al., 2005b)	ND	0.6 (LC50) (Minagh et al., 2009)	25.20 (LC50) (Isidori et al., 2005a)
Tisbe battagliai	48 h	59 (LC50) (Trombini et al., 2016)	ND	ND	ND	ND	ND	ND	ND
Vibrio fischeri	5 min	52.5 (EC50) (Kim et al., 2007)	ND	ND	ND	ND	ND	10.72 (EC50) (Minagh et al., 2009)	ND

	15 min	ND	ND	ND	ND	ND	ND	9.2 (EC50) (Minagh et al., 2009)	43.56 (EC50) (De García et al., 2014)
		28.3 (EC50) (Harada et al., 2008)	ND	ND	ND	ND	ND	ND	78.1 (EC50) (Kim et al., 2007)
		52.2 (EC50) (Kim et al., 2007)	ND	ND	ND	ND	ND	ND	ND
		78.44 (EC50) (Jos et al., 2003)	ND	ND	ND	ND	ND	ND	ND
	30 min	ND	ND	ND	>3000 mg/L (EC50) (Toolaram et al., 2017)	ND	ND	7.3 (EC50) (Minagh et al., 2009)	23.3 (EC50) (Isidori et al., 2005a)
	24 h	ND	ND	ND	ND	ND	0.014 (EC50) (Backhaus et al. 2000)	ND	ND
		ND	ND	ND	ND	ND	0.013 (EC50) (Backhaus & Grimme, 1999)	ND	ND

Table 2.19. Lethal effects of priority personal care products, organized by compound, organism, and exposure time. Lethal concentrations selected for calculating SD indicated in grey. Concentrations are expressed in mg/L. ND=No Data.

Names of the aquatic organisms	Exposure times (min/h/d)	Acute median effective/inhibitory/lethal concentrations (E/I/LC50s)			
		Bisphenol A	Linear alkylbenzene sulfonate	Nonylphenol	Triclosan
Bombina orientalis	96 h	ND	ND	0.24 (LC50) (Park et al., 2010)	ND
Brachionus calyciflorus	24 h	ND	ND	ND	0.345 (LC50) (Zhang et al., 2016)
Caenorhabditis elegans	24 h	ND	ND	ND	3.65 (LC50) (Lenz et al., 2017)
Ceriodaphnia dubia	24 h	ND	ND	ND	0.2 (LC50) (Orvos et al., 2002)
	48 h	ND	21.82 (LC50) (C10)* 9.47 (LC50) (C11) 3.0 (LC50) (C12) 1.85 (LC50) (C13) 0.85 (LC50) (C14) (Belanger et al., 2016)	0.22 (EC50) (Isidori et al., 2006)	ND
Chironomus tentans	96 h	2.7 (EC50) (Mihaich et al., 2009)	ND	ND	ND
Chironomus riparius	48 h	2.64 (LC50) (Lee et al., 2018)	ND	ND	ND
		6.03 (LC50) (Lee & Choi, 2007)	ND	ND	ND
	10 d	11.51 (LC50) (Segner et al., 2003)	ND	ND	ND
Chlamydomonas reinhardtii	24 h	ND	ND	ND	4.26 (EC50) (González-Pleiter et al., 2017)
Corophium volutator	96 h	ND	ND	1.67 (LC50) (Brown et al., 1999)	ND
Crassostrea angulata	24 h	1583.78 ± 125.37 (mean ± SD) (LC50) (Luo et al., 2017)	ND	ND	ND
	48 h	379.25 ± 53.73 (mean ± SD) (LC50) (Luo et al., 2017)	ND	ND	ND
	72 h	98.36 ± 17.29 (mean ± SD) (LC50) (Luo et al., 2017)	ND	ND	ND
	96 h	26.86 ± 3.92 (mean ± SD) (LC50) (Luo et al., 2017)	ND	ND	ND
Cyclotella caspia	96 h	ND	ND	0.18 (EC50) (Liu et al., 2013)	ND
Cymbella sp	24 h	ND	ND	ND	0.625 (EC50) (Ding et al., 2018)

	48 h	ND	ND	ND	0.240 (EC50) (Ding et al., 2018)
	72 h	ND	ND	ND	0.324 (EC50) (Ding et al., 2018)
Cyprinus carpio	96 h	ND	4.4 (LC50) (Wakabayashi et al., 1984)	ND	ND
Danio rerio	48 h	15.9 (LC50) (Tisler et al., 2016)	14.37 (LC50) (Shao et al., 2019)	ND	1.5 (LC50) (Zhou et al., 2019a)
		3.6 (EC50) (Missing body pigmentation) (Tisler et al. 2016)	ND	ND	1.14 (LC50) (Shao et al. 2019)
		12.3 (EC50) (Missing body flow) (Tisler et al., 2016)	ND	ND	0.42 (LC50) (Oliveira et al., 2009)
		13.9 (EC50) (Pericardial edema) (Tisler et al., 2016)	ND	ND	1.34 (LC50) (Zhu et al., 2018)
	72 h	15.7 (LC50) (Chan & Chan 2012)	ND	ND	ND
		4.0 (EC50) (Tisler et al., 2016)	ND	ND	ND
	96 h	ND	ND	ND	0.42 (LC50) (Oliveira et al., 2009)
Daphnia magna	24 h	8.57 (EC50) (Brennan et al., 2006)	ND	0.3 (EC50) (Comber et al., 1993)	0.35 (LC50) (Gao et al., 2014)
		8.9 (EC50) (Tisler et al., 2016)	ND	0.38 (EC50) (Isidori et al., 2006)	ND
	48 h	7.3 (EC50) (Tisler et al., 2016)	ND	0.49 (EC50) (Comber et al., 1993)	0.19 (LC50) (Gao et al., 2014)
		7.75 (EC50) (Brennan et al., 2006)	2.71 (EC50) (Lewis & Perry, 1981)	0.190 (EC50) (Naylor, 1995)	0.18 (EC50) (Tamura et al., 2013)
		8.4 (EC50) (Liu et al., 2019)	ND	ND	0.338 (EC50) (Wang et al., 2013)
		10 (EC50) (Alexander et al., 1988)	ND	ND	0.39 (EC50) (Orvos et al., 2002)
		16 (EC50) (Mu et al., 2005)	ND	ND	ND
Desmodesmus subspicatus	24 h	ND	ND	ND	0.002 (EC50) (Orvos et al., 2002)
Diaphanosoma celebensis	48 h	6.8 (LC50) (In et al., 2019)	ND	ND	ND
Dreissena polymorpha	15 d	ND	ND	3.68 (LC50) (Quinn et al., 2006)	ND
	35 d	ND	ND	2.19 (LC50) (Quinn et al., 2006)	ND
	50 d	ND	ND	1.62 (LC50) (Quinn et al., 2006)	ND

Gammarus pulex	24 h	ND	ND	ND	0.57 (LC50) (Gomez-Canela et al., 2016)
	48 h	5.6 (LC50) (Watts et al., 2001)	ND	ND	ND
	10 d	1.49 (LC50) (Segner et al., 2003)	ND	ND	ND
Hydra vulgaris	96 h	6.9 (EC50) (Pascoe et al., 2002)	ND	ND	ND
		6.91 (LC50) (Segner et al., 2003)	ND	ND	ND
		6.9 (LC50) (Watts et al., 2003)	ND	ND	ND
Hyalella azteca	42 d	0.78 (LC50) (Mihaich et al., 2009)	ND	ND	ND
Lemna gibba	7 d	20 (EC50) (Frond density) 22 (EC50) (Frond biomass) 32 (EC50) (Growth rate) (Mihaich et al., 2009)	ND	ND	ND
Lemna minor	72 h	26.94 (EC50) (MubarakAli et al. 2019)	ND	ND	ND
Marisa cornuarietis	96 h	2.24 (LC50) (25°C) >4.03 (LC50) (22°C) (Mihaich et al., 2009)	ND	ND	ND
Microcystis aeruginosa	72 h	ND	10 (EC50) (Yamane et al., 1984)	ND	ND
	96 h	ND	ND	ND	0.009 (EC50) (Huang et al., 2016)
Misgurnus anguillicaudatus	96 h	ND	ND	ND	0.045 (LC50) (Wang et al., 2013)
Navicula sp	24 h	ND	ND	ND	0.173 (EC50) (Ding et al., 2017)
	72 h	ND	ND	ND	0.145 (EC50) (Ding et al., 2017)
Oncorhynchus mykiss	24 h	ND	ND	0.229 (EC50) (Spehar et al., 2010)	ND
	48 h	ND	ND	0.221 (EC50) 0.257 (LC50) (Spehar et al., 2010)	ND
	72 h	ND	ND	0.116 (EC50) 0.229 (LC50) (Spehar et al., 2010)	ND
	96 h	ND	ND	0.109 (EC50) 0.221 (LC50) (Spehar et al., 2010)	ND
Oryzias latipes	72 h	6.8 (LC50) (Kashiwada et al., 2002)	ND	ND	ND

		7.5 (LC50) (Adults) 5.1 (LC50) (Embryos) (Tabata et al., 2001)	ND	ND	ND
	96 h	13.9 (LC50) (Ishibashi et al., 2005)	ND	ND	0.210 (LC50) (Tamura et al., 2013)
		13 (LC50) (Yokota et al. 2000)	ND	ND	ND
Penicillium expansum	48 h	ND	ND	20 (EC50) (Kuzikova et al., 2017)	ND
Perna perna	48 h	ND	ND	ND	0.13 (IC50) (embryo-larval development assay) 0.49 (IC50) (fertilization assay) (Cortez et al., 2012)
Pimephales promelas	24 h	ND	ND	ND	0.36 (LC50) (Orvos et al., 2002)
	48 h	ND	ND	0.096 (EC50) (Spehar et al., 2010)	0.27 (LC50) (Orvos et al., 2002)
	72 h	ND	ND	0.096 (EC50) 0.134 (LC50) (Spehar et al., 2010)	0.27 (LC50) (Orvos et al., 2002)
	96 h	4.7 (LC50) (Static) 4.6 (LC50) (Flow) (Alexander et al., 1988)	16.58 (LC50) (C10) 7.08 (LC50) (C11) 1.63 (LC50) (C12) 0.63 (LC50) (C13) 0.26 (LC50) (C14) (Belanger et al., 2016)	0.096 (EC50) 0.128 (LC50) (Spehar et al., 2010)	0.26 (LC50) (Orvos et al., 2002)
		ND	ND	0.136 (LC50) (TenEyck & Markee, 2007)	ND
Planktothrix agardhii	4 d	ND	ND	1.5 (EC50) (Medvedeva et al., 2017)	ND
Poecilia reticulata	72 h	1.6 (LC50) (Silva et al., 2018)	ND	ND	ND
	96 h	ND	ND	0.475 (LC50) (Li, 2008)	ND
Poecilia vivipara	96 h	ND	ND	ND	0.6 (LC50) (Escarrone et al., 2016)
Pomacea lineata.	48 h	7.36 (LC50) (Neonates) 22.75 (LC50) (Adults) (De Andrade et al., 2017)	ND	ND	ND
	96 h	3.14 (LC50) (Neonates) 11.09 (LC50) (Adults) (De Andrade et al., 2017)	ND	ND	ND
Pseudochromis fridmani	96 h	ND	ND	0.175 (LC50) (Hamlin et al., 2015)	ND
Pseudokirchneriella subcapitata	24 h	9 (EC50) (Growth rate) 15 (EC50) (Photosynthesis) (Vermeirssen et al., 2017)	ND	ND	ND

	72 h	ND	ND	ND	0.00053 (IC50) (Yang et al., 2008)
		ND	ND	ND	0.0051 (EC50) (Tamura et al., 2013)
	96 h	2.7 (EC50) (Growth) 3.1(EC50) (Cell count) (Alexander et al., 1988)	ND	ND	0.012 (EC50) (Harada et al., 2008)
Salmo trutta	48 h	ND	ND	ND	2.9 (LC50) (Hattula et al., 1981)
Scenedesmus obliquus	72 h	ND	8.8 (EC50) (Volume based growth) 2.6 (EC50) (Chlorophyll-a-based growth) 11.1 (EC50) (photosystem II efficiency) (Lurling, 2006)	ND	ND
	96 h	ND	8.8 (EC50) (Volume based growth) 2.6 (EC50) (Chlorophyll-a-based growth) 11.1 (EC50) (photosystem II efficiency) (Lurling, 2006)	ND	ND
Selenastrum capricornutum	48 h	ND	50 (EC50) (Yamane et al., 1984)	ND	ND
	96 h	2.7 (EC50) (Cell count) 3.1 (EC50) (Cell volume) (Alexander et al., 1988)	ND	ND	0.004 (EC50) (Orvos et al., 2002)
Skeletonema costatum	96 h	1.0 (EC50) (Cell count) 1.8 (EC50) (Chlorophyll a content) (Alexander et al., 1988)	ND	ND	ND
Tetrahymena pyriformis	24 h	608.85 (EC50) (Lang & Kohidai, 2012)	ND	ND	ND
Tetrahymena thermophila	24 h	ND	ND	ND	1.063 (EC50) (Gao et al., 2015)
		ND	ND	ND	1.33 ± 0.16 (mean ± 95% confidence interval) (EC50) (Carbajo et al., 2014)
Thamnocephalus platyurus	24 h	ND	ND	ND	0.470 (LC50) (Kim et al., 2009)
Vibrio fischeri	30 min	4.2 (EC50) (Tisler et al., 2016)	ND	0.48 (EC50) (Hernando et al., 2007)	0.228 ± 0.034 (mean ± 95% confidence interval) (EC50) (Carbajo et al., 2014)
Xenopus laevis	96 h	ND	ND	ND	0.259 (LC50) (Palenske et al., 2010)
Xiphophorus hellerii	96 h	17.9 (LC50) (Kwak et al., 2001)	ND	ND	1.48 (LC50) (Liang et al., 2013)

Note: * - C10: Linear alkylbenzene sulfonate consists of linear chain length of 10 carbon atoms.

Priority PPCPs were reported to produce lethal effects on 60 aquatic organisms after exposure to a range of concentrations (0.00053 to >3000 mg/L) and exposure times (5 min to 50 d). Carbamazepine was widely tested with lethal effects reported for 18 aquatic organisms at concentrations ranging from 3.76 to 1339.43 mg/L and exposure times from 5 min to 144 h (Table 2.18). The lowest reported exposure time showing lethal effects of carbamazepine was 5 min for ultrasensitive *Vibrio fischeri*, reporting a lethal concentration of 52.5 (EC50) mg/L (Kim et al., 2007). Lethal effects of erythromycin were reported for 10 aquatic organisms at concentrations ranging from 0.02 to 387.7 mg/L and exposure times from 24 to 96 h (Table 2.18). The lowest reported exposure time showing lethal effects of erythromycin was 24 h for *Brachionus calyciflorus, Daphnia magna,* and *Thamnocephalus platyurus,* reporting lethal concentrations of 27.53 (LC50), 22.45 (EC50) and 17.68 (LC50) mg/L, respectively (Isidori et al., 2005a).

Fluoxetine was widely tested with lethal effects reported for 13 aquatic organisms at concentrations ranging from 0.044 to 438 mg/L and exposure times from 24 to 96 h (Table 2.18). The lowest reported exposure time showing lethal effects of fluoxetine was 24 h for *Thamnocephalus platyurus,* reporting lethal concentration of 0.76 (LC50) mg/L (Nałecz-Jawecki, 2007). Lethal effects of metoprolol were reported for six aquatic organisms at concentrations ranging from 8.8 to >3000 mg/L and exposure times from 30 min to 7 d (Table 2.18). The lowest reported exposure time showing lethal effects of metoprolol was 30 min for *Vibrio fischeri*, reporting lethal concentration of >3000 (EC50) mg/L (Toolaram et al., 2017).

Lethal effects of naproxen were reported for 10 aquatic organisms at concentrations ranging from 2.62 to 269.15 mg/L and exposure times from 24 to 96 h (Table 2.18). The lowest reported exposure time showing lethal effects of naproxen was

24 h for *Brachionus calyciflorus, Hydra magnipapillata,* and *Thamnocephalus platyurus,* reporting lethal concentrations of 62.48 (LC50), 51.99 (LC50) and 84.09 (LC50) mg/L, respectively (Isidori et al., 2005b; Yamindago et al., 2019). Sertraline was widely tested with lethal effects reported for 13 aquatic organisms at concentrations ranging from 0.004 to 10.72 mg/L and exposure times from 5 min to 21 d (Table 2.18). The lowest reported exposure time showing lethal effects of sertraline was 5 min for ultrasensitive *Vibrio fischeri*, reporting lethal concentration of 10.72 (EC50) mg/L (Minagh et al., 2009).

Sulfamethoxazole was widely tested with lethal effects reported for 15 aquatic organisms at concentrations ranging from 0.0062 to 890.0 mg/L and exposure times from 30 min to 7 d (Table 2.18). The lowest reported exposure time showing lethal effects of sulfamethoxazole was 30 min for ultrasensitive *Vibrio fischeri*, reporting lethal concentration of 43.56 (EC50) mg/L (De García et al., 2014). Similarly, bisphenol A was widely tested with lethal effects reported for 22 aquatic organisms at concentrations ranging from 0.78 to 1583.78 ±125.37 (mean ±SD) mg/L and exposure times from 30 min to 42 d (Table 2.19). The lowest reported exposure time showing lethal effects of bisphenol A was 30 min for ultrasensitive *Vibrio fischeri*, reporting lethal concentration of 4.2 (EC50) mg/L (Tisler et al., 2016).

Lethal effects of linear alkylbenzene sulfonate were reported for eight aquatic organisms at concentrations ranging from 0.26 to 50 mg/L and exposure times from 48 to 96 h (Table 2.19). The lowest reported exposure time showing lethal effects of linear alkylbenzene sulfonate was 48 h for *Ceriodaphnia dubia, Danio rerio, Daphnia magna,* and *Selenastrum capricornutum*, reporting lethal concentrations of 21.82 (LC50), 14.37 (LC50), 2.71 (EC50) and 50 (EC50) mg/L, respectively (Lewis & Perry, 1981; Yamane et al., 1984; Belanger et al., 2016; Shao et al., 2019).

Nonylphenol was widely tested with lethal effects reported for 13 aquatic organisms at concentrations ranging from 0.096 to 20 mg/L and exposure times from 30 min to 50 d (Table 2.19). The lowest reported exposure time showing lethal effects of nonylphenol was 30 min for ultrasensitive *Vibrio fischeri*, reporting lethal concentration of 0.48 (EC50) mg/L (Hernando et al., 2007). Triclosan was the most widely tested PPCP with lethal effects reported for 24 aquatic organisms at concentrations ranging from 0.00053 to 4.26 mg/L and exposure times from 30 min to 96 h (Table 2.19). The lowest reported exposure time showing lethal effects of triclosan was 30 min for ultrasensitive *Vibrio fischeri*, reporting lethal concentration of 0.228 ±0.034 (mean ±95% confidence interval) (EC50) mg/L (Carbajo et al., 2014). Thus, a wide range of lethality of PPCPs was observed in diverse aquatic organisms after exposure to a range of concentrations and exposure times.

2.3.7 Summary assessment of lethal effects of PPCPs on aquatic organisms

Lethal effects on 60 aquatic organisms were widely studied for most priority PPCPs, except for ofloxacin. Some priority PPCPs were reported to produce lethal effects in a relatively higher number of aquatic organisms, such as carbamazepine (n=18), sulfamethoxazole (n=15), bisphenol A (n=22), and triclosan (n=24). Among widely studied priority PPCPs, narrow ranges of thresholds of lethal concentrations were reported for naproxen and linear alkylbenzene sulfonate only. The ranges of lethal concentrations for naproxen was 2.62 to 269.15 mg/L reported in nine studies and 10 to 269.15 mg/L reported in eight studies; and, for linear alkylbenzene sulfonate, the ranges of lethal concentrations was 0.26 to 50 mg/L reported in six studies and 2.6 to 50 mg/L reported in five studies. Thus, there was some level of consensus for naproxen for range of lethal concentrations reported in eight studies and for linear alkylbenzene sulfonate for

range of lethal concentrations reported in five studies, with a difference of one orders of magnitude.

Overall, this reflects weak consensus among the lethal concentrations reported for most priority PPCPs. However, reported lethal concentrations for each PPCP depend also on the sensitivity of the aquatic organism exposed, and therefore a range of lethal concentrations can result from a range of sensitivity among the different organisms. For most reported organisms there was only one study with same exposure (time, concentration) for the same PPCP. In cases where three or more studies reported lethal effects of PPCP compounds from the same exposure on the same organism, mean (±SD) lethal concentrations were calculated (see Table 2.20 for mean ±SD lethal concentrations). In most cases there were wide variations in lethal concentrations for the same PCPP, same organism and same exposure. However, strong consensus exists in lethal concentrations of bisphenol A and triclosan reported for *Daphnia magna* and carbamazepine reported for *Vibrio fischeri*. For example, EC50 concentrations reported for *Daphnia magna* at 48 h exposure, ranged from 7.3 to 16 mg/L (mean= 8.09 ±4.1 mg/L) for bisphenol A (n=5) and from 0.18 to 0.39 mg/L (mean= 0.3 ±0.1 mg/L) for triclosan (n=3); and, EC50 concentrations reported for *Vibrio fischeri* at 15 min exposure, ranged from 28.3 to 78.44 mg/L (mean= 52.98 ±25.08 mg/L) for carbamazepine (n=3). Conversely, there was poor consensus in EC50 concentrations reported for *Daphnia magna* at 48 h exposure, ranged from 13.8 to 111.0 mg/L (mean= 74.21 ±52.73 mg/L) for carbamazepine (n=3), from 7.80 to 210.57 mg/L (mean= 142.05 ±116.28 mg/L) for erythromycin (n=3), from 25 to 166.53 mg/L (mean= 80.84 ±62.20 mg/L) for naproxen (n=4), and from 4.5 to 205.2 mg/L (mean= 119.46 ±82.76 mg/L) for sulfamethoxazole

(n=5). EC50 concentrations for *Pseudokirchneriella subcapitata* at 72 h exposure, ranged from 0.02 to 0.35 mg/L (mean= 0.136 ±0.187 mg/L) for erythromycin (n=3) (Table 2.20).

Some aquatic organisms consistently exhibited lethal effects after exposure to the majority of priority PPCPs (Tables 2.19 and 2.20). For example, lethal effects were reported for *Ceriodaphnia dubia* after exposure to a range of concentrations of carbamazepine, erythromycin, fluoxetine, naproxen, ofloxacin, sulfamethoxazole, linear alkylbenzene sulfonate, and nonylphenol. For *Daphnia magna*, lethal effects were reported after exposure to a range of concentrations of carbamazepine, erythromycin, fluoxetine, metoprolol, naproxen, sertraline, sulfamethoxazole, bisphenol A, linear alkylbenzene sulfonate, nonylphenol, and triclosan. For *Pimephales promelas,* lethal effects were reported after exposure to a range of concentrations of carbamazepine, erythromycin, fluoxetine, sertraline, sulfamethoxazole, bisphenol A, nonylphenol, linear alkylbenzene sulfonate, and triclosan. For *Pseudokirchneriella subcapitata,* lethal effects were reported after exposure to a range of concentrations of carbamazepine, erythromycin, fluoxetine, metoprolol, naproxen ofloxacin, sertraline, sulfamethoxazole, bisphenol A, and triclosan.

Generally, measured environmental concentrations of PPCPs are lower than lethal concentrations (Straub, 2013). Hence, PPCPs are considered to pose a low lethality risk in the natural environment (Ros et al., 2018). However long-term exposure of aquatic organisms to PPCPs in the environment are poorly studied (Sanderson et al., 2004; Mansour et al., 2016). Therefore, chronic toxicity studies focussing on long term exposure to environmentally relevant concentrations of PPCPs are required to thoroughly explore the ecotoxicity of PPCPs (Ros et al., 2018).

2.3.8 Calculation of standard deviation (SD)

Standard deviations were calculated where a minimum of three lethal concentrations were obtained for single species, for the same PPCP compound, and for the same exposure time (see highlighted cells in grey in Tables 2.18 and 2.19). In this review, SDs were calculated using EC50 values in eight instances (Table 2.20):

1. *Daphnia magna* exposed to carbamazepine, erythromycin, naproxen, sulfamethoxazole, bisphenol A, and triclosan for 48 h, respectively;
2. *Pseudokirchneriella subcapitata* exposed to erythromycin for 72 h; and,
3. *Vibrio fischeri* exposed to carbamazepine for 15 min.

Table 2.20. Calculation of mean and standard deviations (SD) for EC50 values expressed in mg/L.

Daphnia magna **exposed to carbamazepine for 48 h**	***Daphnia magna*** **exposed to erythromycin for 48 h**	***Daphnia magna*** **naproxen for 48 h**	***Daphnia magna*** **exposed to sulfamethoxazole for 48 h**	***Daphnia magna*** **exposed to bisphenol A for 48 h**	***Daphnia magna*** **exposed to triclosan for 48 h**	***Pseudokirchneriella subcapitata*** **exposed to erythromycin for 72 h**	***Vibrio fischeri*** **exposed to carbamazepine for 15 min**
a. 13.8 (Ferrari et al. 2003) **b.** 97.82 (Jos et al. 2003) **c.** 111.0 (Sanderson et al. 2003)	**a**. 7.80 (Sanderson et al. 2003) **b**. 207.8 (Ji et al. 2012) **c.** 210.57 (Di Delupis et al. 1992)	**a.** 25 (Bostrom and Berglund 2015) **b.** 46.72 (Gheorghe et al. 2016) **c.** 85.34 (Kwak et al. 2018) **d.** 166.3 (Cleuvers 2004)	**a**. 4.5 (Sanderson et al. 2003) **b.** 75.3 (Osorio et al. 2016) **c**. 123.1 (Park and Choi 2008) **d.** 189.2 (Kim et al. 2007) **e.** 205.2 (Jung et al. 2007)	**a.** 7.3 (Tisler et al. 2016) **b**. 7.75 (Brennan et al. 2006) **c.** 8.4 (Liu et al. 2019) **d**. 10 (Alexander et al. 1988) **e**. 16 (Mu et al.2005)	**a.** 0.18 (Tamura et al. 2013) **b**. 0.338 (Wang et al. 2013) **c**. 0.39 (Orvos et al. 2002)	**a.** 0.02 (Isidori et al. 2005a) **b**. 0.35 (González-Pleiter et al. 2013) **c**. 0.038 (Machado and Soares 2019)	**a.** 28.3 (Harada et al. 2008) **b**. 52.2 (Kim et al. 2007) **c.** 78.44 (Jos et al. 2003)
Mean = 74.21	**Mean** = 142.05	**Mean** = 80.84	**Mean** = 119.46	**Mean** = 8.09	**Mean** = 0.30	**Mean** = 0.136	**Mean** = 52.98
SD = 52.73	**SD** = 116.28	**SD** = 62.20	**SD** = 82.76	**SD** = 4.10	**SD** = 0.1	**SD** = 0.187	**SD** = 25.08

2.3.9 Threshold concentrations of PPCPs for key aquatic species

Threshold concentrations were identified for the 10 most studied aquatic species for toxicity of PPCPs. These species included *Daphnia magna*, *Danio rerio, Vibrio fischeri, Pseudokirchneriella subcapitata, Oncorhynchus mykiss, Oryzias latipes, Ceriodaphnia dubia, Pimephales promelas, Hydra attenuata,* and *Brachionus calyciflorus* (Table 2.5). Threshold concentrations were the minimum concentrations of PPCPs at which aquatic organisms exhibited sublethal and lethal effects. Identified threshold concentrations were tabulated and organized by aquatic species and priority PPCPs for sublethal effects (Table 2.21) and lethal effects (Table 2.22). These threshold levels of PPCPs can help in designing management activities by determining the threshold concentrations for the release of PPCPs into aquatic environments.

Table 2.21. Threshold concentrations of priority PPCPs for key aquatic species for sublethal effects. Concentrations are expressed in µg/L. ND=No Data.

Names of aquatic species	Threshold concentrations of priority pharmaceuticals								Threshold concentrations of priority personal care products			
	Carbamazepine	Erythromycin	Fluoxetine	Metoprolol	Naproxen	Ofloxacin	Sertraline	Sulfamethoxazole	Bisphenol A	Linear alkylbenzene sulfonate	Nonylphenol	Triclosan
Daphnia magna	1750 (Kovacevic et al., 2016)	ND	0.36 (Flaherty & Dodson, 2005)	ND	ND	ND	ND	ND	2.0 (Li et al., 2018)	ND	ND	6.25 (Kovacevic et al., 2016)
Danio rerio	1000 (Weichert et al., 2017).	ND	0.02 (Mishra et al., 2017)	25300 (Van den Brandhof & Montforts, 2010).	ND	ND	ND	1.0 (Lin et al., 2014)	0.29 (Chen et al., 2015)	ND	10 (Xia et al., 2010)	0.1 (Parenti et al., 2019)
Vibrio fischeri	0.20 (Aguirre-Martinez et al., 2015)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Pseudokirchneriella subcapitata	150000 (Vernouillet et al., 2010)	38 (Machado & Soares, 2019)	13.49 (Brooks et al., 2003)	ND	ND	ND	ND	ND	ND	ND	ND	ND
Oncorhynchus mykiss	200 (Li et al., 2009)	0.1 (Rodrigues et al., 2016)	3.09 (Gagne et al., 2006)	ND	ND	ND	ND	990 (Laville et al., 2004)	ND	ND	0.5 (Jobling et al., 1996)	0.48 (Capkin et al., 2017)
Oryzias latipes	615000 (Nassef et al., 2010)	ND	ND	ND	ND	ND	ND	ND	10 (Metcalfe et al., 2001)	ND	8.2 (Yokota et al., 2001)	71 (Orvos et al., 2002)

Ceriodaphnia dubia	ND	ND	223 (Brooks et al., 2003)	ND	ND	ND	ND	ND	ND	ND	ND	ND
Pimephales promelas	ND	ND	ND	ND	ND	ND	ND	ND	15 (Schoenfuss et al., 2008)	ND	ND	ND
Hydra attenuata	50000 (Quinn et al., 2008)	ND	ND	50000 (Quinn et al., 2008)	ND	ND	ND	ND	ND	ND	ND	ND
Brachionus calyciflorus	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.1 (Zhang et al., 2016)

Table 2.22. Threshold concentrations of priority PPCPs for key aquatic species for lethal effects. Concentrations are expressed in mg/L. ND=No Data.

Names of aquatic species	Threshold concentrations of priority pharmaceuticals								Threshold concentrations of priority personal care products			
	Carbamazepine	Erythromycin	Fluoxetine	Metoprolol	Naproxen	Ofloxacin	Sertraline	Sulfamethoxazole	Bisphenol A	Linear alkylbenzene sulfonate	Nonylphenol	Triclosan
Daphnia magna	13.8 (EC50) (EC50) (Ferrari et al., 2003)	7.80 (EC50) Sanderson et al., 2003)	0.51 (LC50) (Cunningham et al., 2006)	8.8 (LC50) Cunningham et al., 2006)	10 (EC50) (Bostrom & Berglund, 2015)	ND	0.066 (EC50) (Minagh et al., 2009)	4.5 (EC50) Sanderson et al., 2003)	7.3 (EC50) (Tisler et al., 2016)	2.71 (EC50) (Lewis & Perry, 1981)	0.190 (EC50) (Naylor, 1995)	0.18 (EC50) (Tamura et al., 2013)
Danio rerio	6.25 (LC50) (Zhou et al., 2019a)	ND	8.45 (EC50) (De Farias et al., 2019)	31.0 (EC50) (Van den Brandhof & Montforts, 2010)	98.3 (EC50) (Li et al., 2016b)	ND	ND	ND	3.6 (EC50) (Tisler et al. 2016)	14.37 (LC50) (Shao et al., 2019)	ND	0.42 (LC50) (Oliveira et al., 2009)
Vibrio fischeri	52.5 (EC50) (Kim et al., 2007)	ND	ND	ND	ND	ND	10.72 (EC50) (Minagh et al., 2009)	ND	4.2 (EC50) (Tisler et al., 2016)	ND	0.48 (EC50) (Hernando et al., 2007)	0.228 (Carbajo et al., 2014)
Pseudokirchneriella subcapitata	48.9 (EC50) (Harada et al., 2008)	0.02 (EC50) (Isidori et al., 2005a)	0.044 (IC50) (Johnson et al., 2007)	>320 (EC50) (Cleuvers, 2003)	>80 (EC50) (González -Pleiter et al., 2013)	0.004 (EC50) (Ferrari et al., 2004)	0.012 (IC50) (Johnson et al., 2007)	0.146 (EC50) (Ferrari et al., 2004)	2.7 (EC50) (Alexander et al., 1988)	ND	ND	ND
Oncorhynchus mykiss	19.9 (LC50) (Li et al., 2011)	ND	ND	ND	ND	ND	0.38 (LC50) (Minagh et al., 2009)	27.35 (EC50) (Laville et al., 2004)	ND	ND	0.109 (EC50) (Spehar et al., 2010)	ND

Oryzias latipes	35.4 (LC50) (Kim et al., 2007)	ND	5.5 (LC50) (Nakamura et al., 2008)	31 (LC50) (Van den Brandhof & Montforts, 2010)	ND	ND	ND	>750 (Kim et al., 2007)	6.8 (LC50) (Kashiwada et al., 2002)	ND	ND	ND
Ceriodaphnia dubia	77.7 (EC50) (Ferrari et al., 2003)	10.23 (EC50) (Isidori et al., 2005a)	0.23 (LC50) (Brooks et al., 2003)	ND	66.4 (EC50) Isidori et al., 2005b)	17.41 (LC50) (Isidori et al., 2005a)	ND	15.51 (LC50) (Isidori et al., 2005a)	ND	0.85 (LC50) (Belanger et al., 2016)	0.22 (EC50) (Isidori et al., 2006)	ND
Pimephales promelas	101.0 (EC50) (Sanderson et al., 2003)	61.0 (EC50) (Sanderson et al., 2003)	0.19 (LC50) (Stanley et al., 2007)	ND	ND	ND	0.072 (EC50) (Valenti et al., 2009)	890.0 (EC50) (Sanderson et al., 2003)	4.6 (LC50) (Alexander et al., 1988)	0.26 (LC50) (Belanger et al., 2016)	0.096 (EC50) (Spehar et al., 2010)	0.26 (LC50) (Orvos et al., 2002)
Hydra attenuata	3.76 (EC50) (Quinn et al., 2008)	ND	ND	ND	2.62 (EC50) (Quinn et al., 2008)	ND	ND	ND	ND	ND	ND	ND
Brachionus calyciflorus	ND	0.94 (EC50) (Isidori et al., 2005a)	ND	ND	62.48 (LC50) (Isidori et al., 2005b)	ND	ND	9.63 (EC50) (Isidori et al., 2005a)	ND	ND	ND	0.345 (LC50) (Zhang et al., 2016)

2.3.10 Environmental relevant concentrations of PPCPs

PPCPs are consistently occurring in environment at low concentrations and often detected in reclaimed surface water at concentrations ranging from ng/L to µg/L due to incomplete removal during conventional treatment processes (Chen et al., 2013). The commercial development of liquid chromatography/electrospray ionization (ESI)/tandem MS (LC/MS-MS) has made it possible to detect low levels of PPCPs in environment (Hao et al., 2006). Ranges of concentrations of priority PPCPs occurring in aquatic environments in Canada and worldwide were identified from scientific literature (Table 2.23).

Table 2.23. Environmentally relevant concentrations of priority PPCPs within Canada and worldwide. Concentrations are expressed in ng/L and µg/L. ND=No Data

12 priority PPCPs	Canada (ng/L)	Worldwide (µg/L)
Priority pharmaceuticals		
Carbamazepine	0.20–749 (Hao et al., 2006; Kleywegt et al., 2011; Arnnok et al., 2017)	0.03–11.6 (Aus der beek et al., 2016; Shi et al., 2019)
Erythromycin	0.10–83 (Hao et al., 2006; Kleywegt et al., 2011; Arnnok et al., 2017)	ND
Fluoxetine	0.32–13 (Weston et al., 2001; Arnnok et al. 2017)	0.012–1.4 (Weinberger II & Klaper, 2014).
Metoprolol	5.7–848 (Arnnok et al., 2017; McBean et al., 2018)	ND
Naproxen	22–107 (Boyd et al., 2003; Hao et al ., 2006; Arnnok et al., 2017)	0.050–32 (Aus der beek et al., 2016)
Ofloxacin	ND	0.278–17.7 (Aus der beek et al., 2016)
Sertraline	218 (Arnnok et al., 2017)	0.01∼1 (Hossain et al., 2019; Neuparth et al., 2019)
Sulfamethoxazole	2–284 (Kleywegt et al., 2011; Arnnok et al., 2017)	0.095–29 (Aus der beek et al., 2016)
Priority personal care products		
Bisphenol A	2.1–100 (EC, HC, 2008; Kleywegt et al., 2011)	0.1–1000 (Ribeiro et al., 2019)
Linear alkyl benzene sulfonate	ND	416 (Fox et al., 2000)
Nonylphenol	800–15100 (Lee & Peart, 1995)	0.015–33.231 (Mao et al., 2012)
Triclosan	<6–874 (Boyd et al., 2003; Arnnok et al., 2017; Lalonde et al., 2019).	0.02–20 (Lu et al., 2018)

2.3.11 Water quality guidelines and environmental risk assessments

Federal Environmental Quality Guidelines (FEQGs) are based on toxicological effects of specific chemical substances and provide benchmarks for the quality of the ambient environment. FEQGs can assist in preventing pollution by providing targets for acceptable environmental quality, estimating the significance of concentrations of chemicals currently found in environment for monitoring, and serve as performance measures of the success of risk management actions (ECCC, 2018). FEQGs are developed by the Federal Minister of Environment and Climate Change Canada under the Canadian Environmental Protection Act (CEPA), 1999 (Government of Canada, 1999). FEQGs are similar to the Canadian Council of Ministers of the Environment (CCME) guidelines in determining the benchmarks for the quality of the ambient environment, based exclusively on toxicological effects, and derived following CCME protocols, where data permits. FEQGs are developed to support federal risk management or monitoring activities where the CCME guidelines for the chemical substance have not yet been established or are not reasonably anticipated to be updated in the near future (ECCC, 2018). Currently, among the 12 priority PPCPs, CCME guideline are available for carbamazepine and FEQGs for bisphenol A, nonylphenol, and triclosan (Table 2.24).

Table 2.24. Federal Environmental Quality Guidelines for priority PPCPs for the protection of aquatic life in Canada. Concentrations are expressed in µg/L. NRG= No recommended guideline.

Names of PPCPs	Freshwater	Marine
Priority pharmaceuticals		
Carbamazepine	10	NRG
Priority personal care products		
Bisphenol A	3.5	3.5
Nonylphenol	1.0	0.7
Triclosan	0.47	NRG

Generally, environmental risk assessment (ERA) is conducted by comparing measured/predicted environmental concentration (MEC/PEC) to the toxicologically relevant predicted no-effect concentrations (PNECs). MEC/PEC provide an estimate of external exposure concentration, whereas PNECs are derived based on acute and/or chronic ecotoxicity data (Bayen et al., 2013). For example, fluoxetine was evaluated for ERA within European Union (EU) against the most recent European risk assessment guideline (EMEA, 2006) (Oakes et al., 2010). Naproxen was subjected to ERA based on acute ecotoxicity data for western Europe (Straub & Stewart, 2007). Ofloxacin was evaluated for ERA in France and Germany against the two-tiered European draft guideline (EMEA, 2001) (Ferrari et al., 2004). Sulfamethoxazole was subjected to ERA in Europe and PNEC was derived based on chronic ecotoxicity data following the EU Technical Guidance Document (EC, 2003) and the EU Technical Guidance for Deriving Environmental Quality Standards (EC, 2011) (Straub, 2016). Thus, PNECs derived for various PPCP compounds can be extended to other jurisdictions for aquatic ERA to assess general risks and indicate some specific investigation or risk management activities.

Table 2.25. Predicted no-effect concentrations derived for priority pharmaceuticals for aquatic environmental risk assessments, based on acute and/or chronic ecotoxicity data. Concentrations are expressed in μg/L.

Priority pharmaceuticals							
Carbamazepine	**Erythromycin**	**Fluoxetine**	**Metoprolol**	**Naproxen**	**Ofloxacin**	**Sertraline**	**Sulfamethoxazole**
0.010 (Chronic) Zhou et al., 2019b)	0.040 (Chronic) (Zhou et al., 2019b)	0.012 (Acute) (Oakes et al., 2010)	0.12 (Acute and chronic) (Godoy et al., 2015)	21 (Acute) (Straub & Stewart, 2007)	0.016 (Acute) 0.5 (Chronic) Ferrari et al., 2004)	12.1 (Acute) Johnson et al., 2007)	0.59 (Chronic) (Straub, 2016)

2.3.12 Species sensitivity distributions (SSDs)

A SSD resembles a bell-shaped distribution (on a log scale) reflecting interspecies differences in sensitivity to a chemical (Posthuma et al., 2019). SSDs quantify proportions of species potentially affected in contaminated compartments of environment using sensitivity data of test species (Posthuma & de Zwart, 2012). SSDs are used in environmental protection, assessment, and management practices, for chemicals responsible for pollution in environment. They assist in planning and interpretation of assessments and help to express expected impact magnitudes of pollution (Posthuma et al., 2019).

A list of aquatic species and stressor intensities are identified to generate SSDs. Stressor intensities are exposure concentrations at which species exhibit a standard response to a stressor (Posthuma et al., 2019). Standard response can be immobilization or death of organisms after exposure to EC50 or LC50 concentrations, respectively. First, ranking is assigned to stressor concentrations from lowest to highest and then ranks are converted to proportions by using the following equation: Proportion=(Rank-0.5)/Number of Species. A linearized log-normal curve is obtained by placing stressor intensity on X-axis and proportions of species affected on Y-axis (US EPA, 2005). Further, proportions are converted to probit, which are inverse cumulative distribution function of the normal distribution with a mean of 5 and a standard deviation of 1. A mean of 5 is selected to make sure that all probit values are non-negative. A central tendency is obtained by regressing Log 10 concentrations (X-axis)*probit (Y-axis) (US EPA, 2005).

As per the interpretation of SSDs, randomly selected species from the set of tested species would be exposed beyond the chronic or acute no-effect level of species. Potentially affected fraction of species is identified, as higher toxic pressures affect higher

fractions of species for the studied acute or chronic endpoints. Impact distributions across water bodies are investigated using the same data to classify water bodies as "insufficiently protected". Relative impact contributions of different chemicals are investigated, which also helps to identify chemicals that likely affect ecosystems and not identified by monitoring (Posthuma et al., 2019). However, there are limitations of SSD-based assessments, as food chain exposures and indirect effects are not taken into considerations in SSDs. Moreover, the assessor should be aware of the fact that aquatic species exposed to toxic pressure in a water body exhibit widely different impacts, resulting in complex interpretations, related to species sensitivity differences that form the basis for SSDs (Posthuma et al., 2019).

In this review, SSDs were generated using EC50 values reported after exposure of different aquatic species to carbamazepine for 48 h (Fig. 2.2) and LC50 values reported after exposure to triclosan for 24 h (Fig. 2.3), respectively.

Table 2.26. EC50s (stressor intensities) after exposure to carbamazepine for 48 h, followed by calculated values of proportion, probit, central tendency, upper and lower predicted interval (PI). EC50s are expressed in mg/L.

Names of aquatic species	EC50 (stressor intensity)	Log 10 EC50	Rank	Proportion	Probit	Central Tendency	Upper PI (95% Prediction Interval)	Lower PI (95% Confidence Interval)
Ceriodaphnia dubia	77.7 (Ferrari et al., 2003)	1.8904	6	0.79	5.7916	88.860	152.752	51.693
Chlorella pyrenoidosa	239.84 (Zhang et al., 2012)	2.3799	7	0.93	6.4652	118.505	207.363	67.724
Chlorella vulgaris	36.62 (Jos et al., 2003)	1.5637	2	0.21	4.2084	17.255	31.315	9.507
Danio rerio	46.53 (Weichert et al., 2017)	1.6677	3	0.36	4.6339	25.722	45.008	14.700
Daphnia magna	13.8 (Ferrari et al., 2003)	1.1399	1	0.07	3.5348	12.408	23.415	6.576
Pseudokirchneriella subcapitata	48.9 (Harada et al., 2008)	1.6893	4	0.5	5.0000	43.870	74.747	25.747
Scenedesmus obliquus	72.97 (Zhang et al., 2012)	1.8631	5	0.64	5.3661	55.210	93.814	32.491

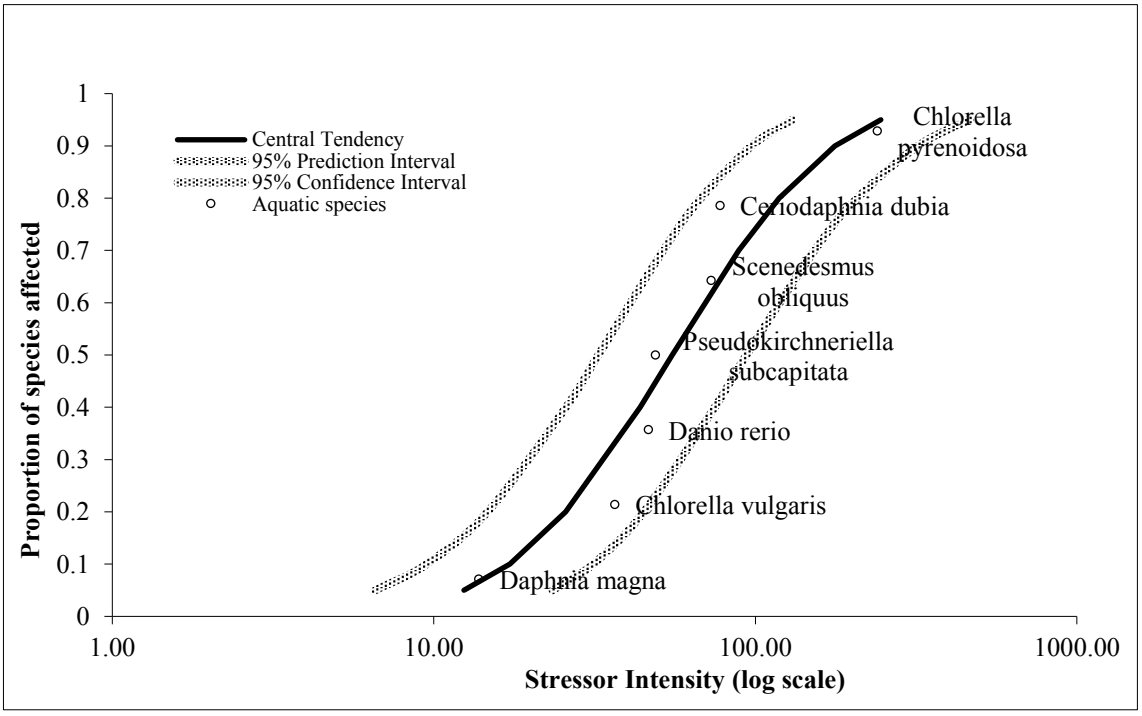

Figure 2.2. Species sensitivity distribution curve for carbamazepine**.**

Table 2.27. LC50s (stressor intensities) after exposure to triclosan for 24 h, followed by calculated values of proportion, probit, central tendency, upper and lower predicted interval (PI). LC50s are expressed in mg/L.

Names of aquatic species	LC50 (stressor intensity)	Log 10 LC50	Rank	Proportion	Probit	Central Tendency	Upper PI (95% Prediction Interval)	Lower PI (95% Confidence Interval)
Brachionus calyciflorus	0.345 (Zhang et al., 2016)	-0.4622	2	0.21	4.2084	0.125	0.536	0.029
Caenorhabditis elegans	3.65 (Lenz et al., 2017)	0.5623	7	0.93	6.4652	1.265	4.865	0.329
Ceriodaphnia dubia	0.2 (Orvos et al., 2002)	-0.6990	1	0.07	3.5348	0.084	0.404	0.018
Daphnia magna	0.35 (Gao et al., 2014)	-0.4559	3	0.36	4.6339	0.202	0.778	0.053
Gammarus pulex	0.57 (Gomez-Canela et al., 2016)	-0.2441	6	0.79	5.7916	0.896	3.269	0.245
Pimephales promelas	0.36 (Orvos et al., 2002)	-0.4437	4	0.50	5.0000	0.384	1.365	0.108
Thamnocephalus platyurus	0.470 (Kim et al., 2009)	-0.3279	5	0.64	5.3661	0.506	1.785	0.144

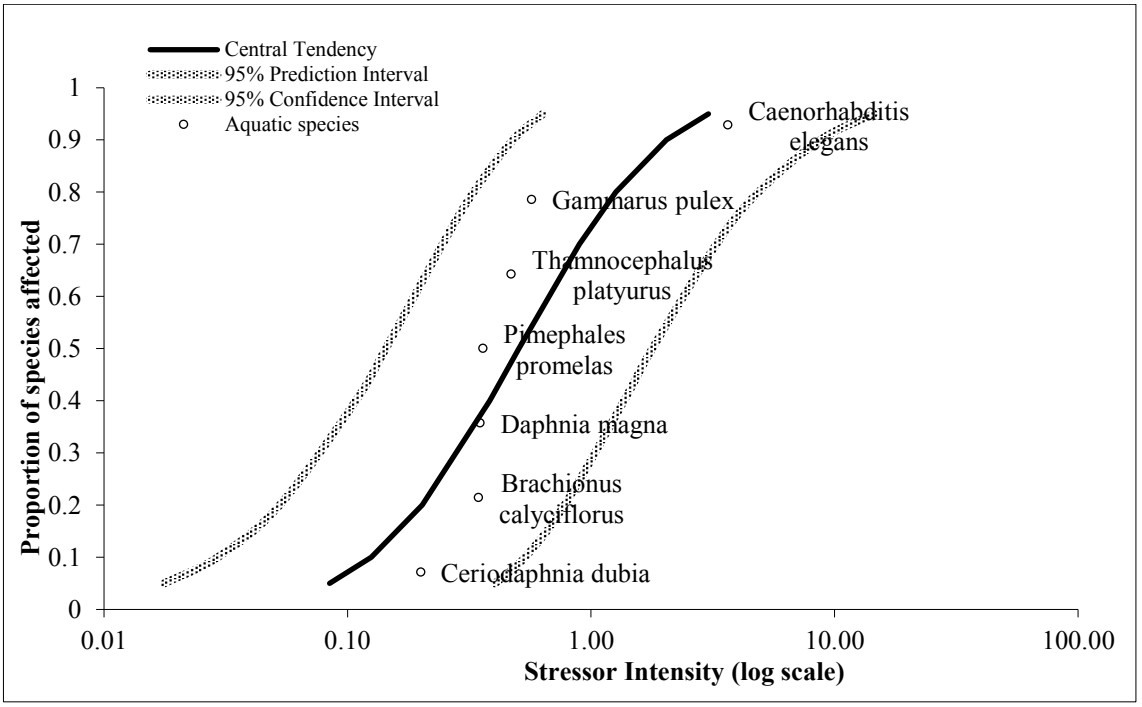

Figure 2.3. Species sensitivity distribution curve for triclosan.

2.4 Discussion

Overall, a large number (n=16,938) of studies on aquatic toxicity of 12 priority PPCPs were identified in this review, supporting the view that aquatic toxicity of PPCPs is widely studied. However, the full scope, magnitude, and implications of the presence of PPCPs in the aquatic environment are largely understudied, as recognized by Daughton (2001).

This review shows that sublethal toxicity threshold ranges for some organisms and some PPCPs can be identified by comparing reported measures of the effects in aquatic organisms, such as by measuring the behavioural alterations, as noted by Kane et al. (2004) and Nassef et al. (2010). However, only a small number of PPCPs have been subjected to complete risk assessments where appropriate sublethal endpoints are included. Hence, the information associated with the toxicity of PPCPs remains limited in the context of their potential environmental concern, as identified by Martin-Diaz et al. (2009). Therefore, more specific endpoints and chronic exposure studies are required for a thorough risk assessment of PPCPs, as recommended by Ferrari et al. (2003).

Studies have reported the presence of numerous PPCPs in aquatic environments throughout the world (Kolpin et al., 2002; Kasprzyk-Hordern et al., 2008; Stewart et al., 2014). However, the majority of PPCPs are largely understudied, yet have been determined to be low risk and thus unregulated, as identified by Richmond et al. (2017). Most of the research conducted on adverse effects of PPCPs are based on traditional toxicity tests conducted in laboratory settings. These toxicity tests include determining ecotoxicity concentrations of PPCPs, such as EC50s, LC50s, and PNECs. These concentrations are much higher than the concentrations detected in environment and therefore many PPCPs are classified nontoxic. However, negative effects on organisms

are reported at much lower, sublethal concentrations. Hence, toxicity studies based on traditional lethal toxicity testing may underestimate the potential risks of PPCPs in aquatic environments, as identified by Richmond et al. (2017).

Generally, the death of organisms is the endpoint in acute toxicity testing. However, the death of individuals after short-term exposure to high concentrations is questionable in terms of environmental significance. Concentrations of PPCPs in the environment are not generally found within lethal ranges except following accidental spills. Therefore, chronic toxicity effects after long-term exposure to low concentrations are more environmentally relevant and should be investigated, as recommended by Nagel (2002). Many aquatic organisms are continuously exposed to PPCPs throughout their life cycles. Unintended detrimental impacts on aquatic life may be caused by occurrence of PPCPs in aquatic environments even at low concentrations. Reviewed studies report results that indicate PPCPs are causing sublethal effects in aquatic organisms at exposure levels similar to those currently or likely to occur in environment, as identified by Ebele et al. (2017).

Diverse aquatic organisms were examined to investigate the acute and chronic aquatic toxicity of PPCPs. Organisms like *Daphnia Magna* and *Danio rerio* are largely used in laboratory studies for studying the aquatic toxicity of environmentally detected PPCPs. *Daphnia Magna*, freshwater zooplankton, is sensitive to its chemical environment, has rapid reproduction, and plays a critical role in freshwater ecosystems (Flaherty & Dodson, 2005). The subtle and sublethal effects on the normal life processes of Daphnia are produced at concentrations that are several orders of magnitude lower than lethal concentrations (Dodson et al., 1999). Further, *Danio rerio* (Zebrafish) embryo test is a preferred acute fish test because it is more sensitive than the adult zebrafish and

permanent cell lines derived from *Oncorhynchus mykiss* (Rainbow trout) (Nagel, 2002). Moreover, zebrafish are inexpensive and can be easily obtained and readily maintained under appropriate conditions. It can provide a large number of non-adherent and transparent eggs (Laale, 1977) because one female fish can lay approximately 50-200 eggs per day (Nagel, 1993). However, most aquatic organisms identified as exhibiting sublethal effects of PPCPs at environmentally relevant concentrations and those reported with no effect are largely understudied. There was no PPCP or organism for which there was more than one study reporting on the same sublethal effects for same exposure parameters (time, concentration) for the same PPCP and the same organism. These understudied organisms may have low reproduction rates, sublethal effects produced at higher levels of exposure concentrations, less sensitivity to their chemical environment, and expensive models. Therefore, more studies are warranted on aquatic toxicity of PPCPs involving understudied organisms exhibiting sublethal effects to estimate this ecological problem wholly.

Although more widely studied than sublethal effects, lethal effects are also understudied for many organisms. There were few PPCPs and organisms for which there was more than one study reporting lethal effects for the same exposure parameters (time, concentration). These include EC50 concentrations reported for *Daphnia Magna* upon 48 h exposure to carbamazepine, erythromycin, naproxen, sulfamethoxazole, bisphenol A, and triclosan; EC50 concentrations reported for *Vibrio fischeri* upon 15 min exposure to carbamazepine; and, EC50 concentrations reported for *Pseudokirchneriella subcapitata* upon 72 h exposure to erythromycin. Concentrations reported for these lethal effects vary widely across studies. However, there was relatively low variation in SDs calculated for *Daphnia Magna* (48 h exposure to triclosan and bisphenol A, respectively) and *Vibrio*

fischeri (15 min exposure to carbamazepine) (Table 2.20). Thus, there was consensus among reported thresholds of triclosan and bisphenol A for *Daphnia Magna* and carbamazepine for *Vibrio fischeri* only. Accordingly, there is little corroborating evidence to support identification of threshold levels for most organisms and PPCPs, with possible exceptions where more than one study reported lethal effects for the same exposure parameters (time, concentration). Therefore, further research is needed, particularly on PPCPs that seem to indicate effects across organisms and at low levels, including sublethal effects. However, the synthesis of this review demonstrating sublethal and lethal effects of PPCPs create a preliminary dataset that should continue to be populated as new studies are published, helping to determine consensus as it emerges.

Five most widely studied PPCP compounds for aquatic toxicity were identified in this review. Among them, three pharmaceuticals were carbamazepine, fluoxetine, sulfamethoxazole, which are widely used as an anticonvulsant, antidepressant, and antibiotic, respectively; and two personal care products were bisphenol A and triclosan, which are widely used as a protective lining material in food containers and antimicrobial in personal care products, respectively. These compounds were widely studied for sublethal and lethal effects of PPCPs on diverse aquatic organisms. Therefore, identified threshold (minimum) concentrations of these compounds at which organisms start exhibiting toxic effects in a laboratory- or field-based studies, can be used to design the management strategies to reduce the emission of PPCPs in aquatic environments. It can help to determine the threshold concentrations for the release of PPCPs into aquatic environments.

The release of PPCPs into aquatic environments can be reduced by enhancing the removal of PPCPs from wastewater by equipping WWTPs with the advanced treatment

processes, such as advanced oxidization processes, novel membrane technologies, activated carbon adsorption, and biological treatment processes (Wang & Wang, 2016). For example, carbamazepine is removed above 90% by reverse osmosis and nanofiltration membranes and up to 90–99% with post-treatment with granular and powdered activated carbon (Hai et al., 2018). A high removal rate was observed for some PPCPs through the membrane bioreactor (MBR) system used for treatment in WWTPs Carbamazepine, fluoxetine, naproxen, and sulfamethoxazole were reduced to <10 ng/L from MBR influent concentrations of 281, 44, 70 and 23 ng/L, respectively (Snyder et al., 2007). The removal efficiency of sulfamethoxazole varied between 52–100% in activated sludge process (Li & Zhang, 2011). Bacterial isolates from activated sludge in a WWTPs were able to degrade triclosan and bisphenol A to below 10 ng/L (Zhou et al., 2013). Removal of triclosan from biological and secondary treatment facilities was significantly higher than the primary treatment facilities, analyzed in samples collected from 13 WWTPs across Canada. Median concentrations of triclosan detected in influent and effluent were 1480 and 107 ng/L, respectively. This comprehensive study highlighted the consistent presence of triclosan in wastewater at relatively high concentrations and their removal being strongly influenced by wastewater treatment types (Guerra et al., 2019). Thus, overall environmental concentrations of PPCPs are increasing due to extensive and increasing use. However, a high removal rate of PPCPs from wastewater by advanced treatment processes can reduce their concentrations in aquatic environments.

2.5 Recommendations for future research

To better understand and manage toxic effects produced by PPCPs in aquatic environments, future research is warranted on chronic toxicity, ecological field studies, and mixture effects. Current levels of PPCPs in environment are lower than the threshold effect levels for the traditional ecotoxicological acute assays (Ferrari et al., 2003); however, aquatic organisms are exposed to these low concentrations throughout their entire life span. Chronic toxicity effects accrue over time from exposure to the environmental presence of PPCPs (Crane, Watts & Boucard, 2006). Even though studies on chronic toxicity of PPCPs in diverse aquatic organisms are increasing, this study shows there is a lack of information for many PPCPs and species, consistent with the finding of Carlsson et al. (2006). Chronic toxicity studies are required to investigate the sublethal effects of understudied priority PPCPs (e.g., ofloxacin, sertraline, and linear alkylbenzene sulfonate) on the understudied aquatic species (e.g., *Diopatra neapolitana, Artemia franciscana, Orconectes virilis,* and *Salmo trutta*), and several other PPCPs and aquatic organisms that we did not assessed. Although beyond the scope of this study, the mechanism of action through which chronic toxicity is induced in aquatic organisms and its effect on population dynamics of organisms should be scrutinized. With further studies on chronic toxicity, the ecological hazards of PPCPs for aquatic ecosystems will be able to be more effectively evaluated (Parolini et al., 2013).

PPCPs can enter the environment through several pathways, including both point and non-point sources, and are commonly detected in surface waters at low concentrations (ng/L to µg/L) (Daughton & Ternes, 1999). Accordingly, more ecological studies are required to better understand sublethal effects on various components of aquatic ecosystems. Such studies were largely missing from the publications revealed in

our targeted search for studies on toxicity measures associated with effects on aquatic organisms for the 12 priority PPCPs. PPCPs can cause ecological disruptions directly or indirectly (McQueen, Post & Mills, 1986) by altering the relationship among organisms (Barry, 2014). These ecological effects are largely undetected because many are subtle and difficult to measure. Ecological studies are needed to evaluate the overall effects of PPCPs in aquatic ecosystems (Richmond et al., 2017).

The ecological effects of single PPCP compound exposure may be amplified by simultaneous exposures to a wide range of PPCPs frequently identified in aquatic environments (Bradley et al., 2017). As this review shows, PPCPs continue to be typically analyzed for ecotoxicological effects as single compounds and rarely as mixtures (Cleuvers, 2003; Fernandez, Carbonell & Babin, 2013). However, PPCPs are present in environment as mixtures which may increase overall concentrations of pollutants and produce synergistic effects. Thus, overall toxicity will be produced as a result of the sum of concentrations of individual compounds, and ecotoxicity effects may occur even when individual compounds are present at NOEC levels (Fent, Weston & Caminada, 2006). Initially, it was assumed that only compounds with the same mode of toxic action produce detrimental effects due to concentration additions in mixtures; however, recent studies have shown that mixtures of compounds with different modes of toxic action produce harmful effects in aquatic organisms due to combined toxicity (Altenburger, Walter & Grote, 2004). Further research is warranted on the combined toxicity of PPCPs mixtures on aquatic organisms.

2.6 Conclusion

This chapter reviewed a series of papers on aquatic toxicity to identify the diverse aquatic organisms affected by PPCPs and the variety of sublethal and lethal effects

produced on their exposure to 12 priority PPCPs. This provided an in-depth understanding of ecotoxicity of PPCPs in aquatic organisms, even when present at very low concentrations, such as sublethal effects, wherein environmentally relevant concentrations were identified. Lethal concentrations, which can cause immobilization, inhibition of growth or death of the organisms were identified from laboratory-based studies.

A diverse range of aquatic organisms are affected by the presence of PPCPs at both sublethal and lethal exposures. Aquatic organisms are exhibiting sublethal effects on exposure to environmentally relevant concentrations of PPCPs. This suggests that they may exhibit lethal effects in the future with increases in environmental concentrations of PPCPs. Therefore, there is an urgency to investigate PPCPs in different jurisdictions around the world. Lethal effects were seldom reported in aquatic organisms at environmentally relevant concentrations, and many PPCPs were considered non-toxic based on lethal endpoints. It is likely, however, that PPCP concentrations in the environment will increase in the future to near sublethal and near-lethal ranges for aquatic organisms, except when wastewater treated through advanced wastewater treatment processes. Therefore, more studies testing chronic toxicity of PPCPs on aquatic organisms at environmentally relevant concentrations are required. Further, investigation of the subtle, indirect, and long-term ecological effects of PPCPs in natural aquatic environments is recommended. Additionally, there is a necessity to analyze the mixture effects of PPCPs in aquatic ecosystems. Such measures will help support future research to determine the extent and magnitude of PPCP concentrations in aquatic environments and help inform management decisions to reduce sources of PPCP leakage into the environment.

In the following chapter, final conclusions of thesis findings are presented along with management implications to control the release of PPCPs from various sources into the environment.

CHAPTER 3: Conclusions

3.1 Summary of research

PPCPs consist of numerous categories of chemicals with unique physicochemical properties and biological activities (Boxall et al., 2012). PPCPs enter the environment through multiple pathways. They are directly released into the environment after passing through wastewater treatment processes (WWTPs), which are often not designed to remove PPCPs (Halling-Sørensen et al., 1998). Veterinary pharmaceuticals are released into the environment through overflow along with animal wastes, leakage from manure lagoons, and land application as manure (Meyer et al., 2000; Meyer 2004). Pharmaceuticals such as caffeine, nicotine, and aspirin have been entering the environment for several decades in populated areas through treated and untreated sewage effluents (Daughton, 2001). However, the wider issue of toxic impacts has emerged recently when numerous PPCPs with a wide spectrum of therapeutic actions have been detected in aquatic environments (Bu et al., 2013; Ebele et al., 2017; Zhang et al., 2017). PPCPs may have restricted lifetimes, however their continuous use and release into the aquatic environment, make them pseudo persistent (Daughton & Ternes, 1999), thereby posing threats to organisms exposed to them (Bu et al., 2013). PPCPs tend to bioaccumulate in aquatic organisms (Muir et al., 2017), further increasing the risks associated with PPCPs. A major ecological concern arises from the ability of PPCPs to interfere with the endocrine system of aquatic organisms and produce undesired effects (Fabbri & Franzellitti, 2016). Though numerous concerns are expressed and studies have been conducted, there remains a gap in understanding of concentration levels that produce sublethal and lethal effects in organisms, especially those at environmentally relevant

concentrations. Lack of identified thresholds poses a challenge for risk assessment and environmental policy and management.

3.1.1 Key findings

To understand this problem, this thesis conducted a systematic literature review on aquatic toxicity of PPCPs to identify priority PPCPs, the diverse aquatic organisms reported as affected, and the variety of reported sublethal and lethal effects produced on specified exposures (time, concentration) to priority PPCPs. Specifically, seven key findings emerge from this study.

1. Twelve **priority PPCPs** posing risk of toxicity in the aquatic environments were identified from the most relevant studies for extensive literature review and analysis (Table 2.1).
2. Approximately 300–3385 and 17–85 of **scientific studies** were identified in initial and refined searches, respectively, for each priority PPCP from *Science Direct* database using search strings comprised of specific sets of keywords (Table 2.3).
3. Numerous **aquatic organisms** (n=136) were reported as exhibiting sublethal and lethal effects on exposure to PPCPs by laboratory- and field-based studies (Table 2.4). Organisms reported in large numbers of studies were *Daphnia magna* (n=55), *Danio rerio* (n=43), *Vibrio fischeri* (n=28), *Pseudokirchneriella subcapitata* (n=26), *Oncorhynchus mykiss* (n=17), and *Oryzias latipes* (n=15). Phyla studied for relatively large number of organisms were Arthropoda (n=23), Chordata (n=31), Mollusca (n=20), and Chlorophyta (n=17).
4. **PPCPs most studied** for toxicity on aquatic organisms were bisphenol A (n=114), carbamazepine (n=86), fluoxetine (n=54), sulfamethoxazole (n=52), nonylphenol (n=71), and triclosan (n=68).

5. A range of **sublethal effects** of PPCPs were reported in 79 aquatic organisms after exposure to a range of concentrations (2.30×10^{-5} μg/L to 160 mg/L) and exposure times (5 min to 180 d) (Tables 2.6–2.17). Sublethal effects included behavioral alterations, histological changes, biochemical responses, genotoxicity, and/or cytotoxicity. PPCPs reported to produce sublethal effects in a relatively large number of aquatic organisms were carbamazepine (n=26), bisphenol A (n=19), nonylphenol (n=18), and triclosan (n=17). Two aquatic organisms reported to consistently exhibit sublethal effects after exposure to large number of PPCPs were *Danio rerio* and *Oncorhynchus mykiss.*
6. A range of **lethal effects** of PPCPs were reported in 60 aquatic organisms after exposure to range of concentrations (0.00053 to >3000 mg/L) and exposure times (5 min to 50 d) (Tables 2.18–2.19). Reported lethal effects were investigated by identifying lethal concentrations including EC50, IC50, and LC50, which cause immobilization, inhibition of growth, and/or completely kill the organisms, respectively. PPCPs reported to produce lethal effects in a relatively large number of aquatic organisms were carbamazepine (n=18), sulfamethoxazole (n=15), bisphenol A (n=22), and triclosan (n=24).
7. There was **no PPCP or organism** for which there was more than one study reporting sublethal effects for the same exposure parameters (time, concentration). However, there were a **few PPCPs and organisms** for which there were more than one study reporting lethal effects for the same exposure parameters. For example, *Daphnia magna* exposed to carbamazepine (n=3), erythromycin (n=3), naproxen (n=4), sulfamethoxazole (n=5), bisphenol A (n=5), and triclosan (n=3) for 48 h, respectively; *Pseudokirchneriella subcapitata* exposed to erythromycin (n=3) for 72

hr; and, *Vibrio fischeri* exposed to carbamazepine (n=3) for 15 min. Among them, strong consensus only exists in lethal concentrations reported for *Daphnia magna* exposed to bisphenol A and triclosan for 48 h, respectively and *Vibrio fischeri* exposed to carbamazepine for 15 min (Table 2.20).

It is found that diverse aquatic organisms exhibit a variety of sublethal effects on exposure to environmentally relevant concentrations of PPCPs and may exhibit lethal effects in the future with increases in environmental concentrations of PPCPs. Most aquatic organisms identified as exhibiting sublethal effects at environmentally relevant concentrations and lethal effects in laboratory studies and those reported with no effect are understudied. Understudied organisms reported with no effect may show up effect if studied for wider ranges of exposure concentrations and times. Most of the laboratory-based studies are conducted for a shorter duration of exposure times. However, aquatic organisms are exposed to PPCPs throughout their entire life span in the environment. Toxic effects accrue over time from exposure to the environmental presence of PPCPs (Crane et al., 2006). Moreover, there are few field-based studies conducted on aquatic toxicity of PPCPs. Therefore, more laboratory- and field-based studies are required to be conducted on understudied aquatic species to fully investigate aquatic toxicity of PPCPs.

Overall, there is little corroborating evidence to support identification of threshold levels for most organisms and PPCPs, with possible exceptions where more than one study reported lethal effects for the same exposure parameters (time, concentration). However, this study is an important initial contribution that can be build upon towards understanding the severity of aquatic toxicity of PPCPs. The tables demonstrating sublethal and lethal effects of PPCPs create a preliminary dataset that can continue to be populated as new studies are published, helping to identify consensus as it emerges.

3.1.2 Research gaps

Although the occurrence of PPCPs in aquatic environments is reported throughout the world, most of them are understudied and considered to be of low risk. Most of the research on adverse effects of PPCPs on aquatic organisms is based on traditional lethal toxicity studies conducted in laboratory settings, where death of the organisms is the endpoint. In contrast, concentrations of PPCPs in the environment are not within lethal ranges at present or likely in the short term. Hence, toxicity studies based on traditional lethal toxicity testing underestimate the potential risk of PPCPs in aquatic environments, as identified by Richmond et al. (2017). Therefore, chronic toxicity effects after long-term exposure to low concentrations are more environmentally relevant and should be investigated, as recommended by Nagel (2002).

Further, there is limited knowledge regarding the effects of PPCP mixtures on aquatic organisms, as identified by Dietrich et al. (2010). Aquatic organisms are exposed not only to isolated PPCPs in the environment but to complex chemical mixtures, which might contain individual compounds at concentrations too low to raise concern. However, these mixtures of compounds can produce toxic effects in organisms due to additive and/or synergistic effects and render such mixtures dangerously potent, as found by Schwarzenbach et al. (2006). Hence, analyzing the adverse effects of a single PPCP may underestimate the environmental impacts of PPCPs, as noted by Fernandez et al. (2013). Therefore, more studies are needed on the combined toxicity of PPCPs, analyzing the mixture effects on organisms and in the environment.

Though beyond the scope of this study, there is a lack of solid understanding of fate, bioaccumulation, and tropic magnification of PPCPs in the environment, as identified by Walters et al. (2016), Ebele et al. (2017), and Richmond et al. (2017).

PPCPs are not well studied in the context of ecological and environmental research. The toxicological testing of PPCPs under laboratory conditions is insufficient to predict their individual or collective impacts once they enter aquatic ecosystems and organisms. PPCPs and their metabolites may become either more or less toxic after interacting with a variety of other chemicals in the natural environment or transformation by organisms or exposure to natural light, as found by Bernhardt, Rosi and Gessner (2017). The potential degradation products/metabolites of PPCPs formed in the natural environment or by non-target organisms may be different from those formed under human physiological conditions. There are chances that they may be more toxic/bioaccumulative than the parent PPCPs, as noted by Ebele et al. (2017). Therefore, there is a need for ecological investigations to understand the impacts of PPCPs in the real world in addition to toxicological testing in laboratory settings, as recommended by Halstead et al. (2014), Gessner and Tlili (2016), and Bernhardt et al. (2017).

Overall, little is known about the occurrence, transport, and ultimate fate of PPCPs in the environment. More research is needed into detection, occurrence, fate of PPCPs, and transformation products and metabolites of PPCPs, as recommended by Monteiro and Boxall (2010). This will determine the extent and magnitude of the presence of concentrations of PPCPs in aquatic environments and help with the design of effective management strategies to reduce sources of PPCP emissions into the environment.

3.2 Management implications

The concentrations of PPCPs in aquatic environments will increase with time. They are extensively and increasingly used by humans and continuously released into various compartments of the aquatic environment in the absence of any mechanisms to

remove them during wastewater treatment processes (Nikolaou et al., 2007; Osorio et al., 2016). This will cause adverse effects on aquatic life, and result in detection of more compounds in various aquatic environments (e.g., surface water, groundwater, and seawater) in the future (Kummerer, 2004; Nikolaou et al., 2007). The global human population and percentage of population living in high-density urban areas are increasing continuously. This will substantially increase both the number of PPCP contaminated ecosystems and typical PPCP concentrations found in the environment (Aus der beek et al., 2016). The major point sources responsible for the release of PPCPs into aquatic environments are WWTPs, alongside other sources, such as agricultural runoff and landfill leaching (Daughton & Ternes, 1999; Ebele et al., 2017). Evidence suggests that WWTPs do not remove PPCPs completely during the treatment process (Osorio et al., 2016). Therefore, effective monitoring strategies regarding use, disposal, occurrence, and impacts at different stages of life cycle of PPCPs are required to control their release into the environment (Boxall et al., 2012). Moreover, strict enforcement of stronger regulations with restrictions on identified thresholds for the release of PPCPs into the environment is required. Thus, the presence and fate of PPCPs in the environment is a complicated problem and requires multiple and complementary solutions to address the various concerns (Eckstein, 2012).

These management implications can be efficiently designed by considering identified threshold concentrations of PPCPs for key aquatic species (Tables 2.21 and 2.22). Also, current ranges of environmental relevant concentrations of PPCPs can help design the management strategies to mitigate the release of PPCPs into aquatic ecosystems (Table 2.23). Additionally, water quality guidelines (Table 2.24), PNECs (Table 2.25), and SSDs for PPCPs widely causing aquatic toxicity (e.g., carbamazepine

and triclosan) can be used to determine management practices for controlling chemical pollution caused by PPCPs in aquatic environments.

3.3 Management solutions

3.3.1 Rational use of PPCPs

World Health Organization estimates that more than half of all drugs are prescribed, dispensed, or sold improperly, and approximately half of all patients fail to take them accurately as prescribed by the doctor (Prakash, Nadig & Nayak, 2016). Irrational use of pharmaceuticals includes prescribing too many drugs to a patient, irrational use of antibiotics for non-bacterial infections, overuse of injectables despite suitability of oral formulations, and failure to prescribe as per clinical guidelines (World Health Organization, 2002). Inappropriate prescribing, including overprescribing and misprescribing, which is highly prevalent among older people worldwide (O'Connor, Gallagher & O'Mahony, 2012). Irrational use of pharmaceuticals leads to wastage of scarce resources and their emissions into the environment. Therefore, emphasis should be given on rational use of pharmaceuticals, good prescribing, and dispensing (Ofori-Asenso & Agyeman, 2016).

3.3.2 Advancement in wastewater treatment technologies

It is necessary to develop advanced wastewater treatment technologies to remove PPCPs efficiently from effluents, before releasing into receiving water (Ebele et al., 2017). A review of PPCP removal during wastewater treatment in 14 countries/regions found the percent removal of these compounds was highly variable and depended on PPCP properties (Cizmas et al., 2015). As a result, the application of alternative techniques including membrane processes, activated carbon adsorption, advanced oxidation processes (AOPs), and combinations of them, which may lead to higher

removals, may be necessary before final disposal of effluents or their reuse for irrigation or groundwater recharge (Michael et al., 2013).

3.3.3 Appropriate disposal of PPCPs

The disposal of PPCPs should be controlled and supervised. Disposal of unused or expired medications is the easiest target for source control. They should be properly discarded through collection systems or hazardous waste facilities, rather than flushed down the toilet, washed away in the sink, and disposed of as household trash (Glassmeyer et al., 2009). Hospital wastewater is heavily laden with pharmaceuticals and antibiotic-resistant bacteria. Therefore, a separate treatment of hospital wastewater, such as by using a membrane bioreactor followed by ozonation of the effluent, should be considered (Mahnik et al., 2007). Overall disposal of drugs is a complex function of patient compliance, excretion pharmacokinetics, and packaging, and all of them can vary for each medication (Ruhoy & Daughton, 2007). Though there is insufficient understanding of significance of drug-disposal contribution to the environmental loading of drugs, it is likely that controlling the disposal of certain drugs would reduce their release into the environment (Glassmeyer et al., 2009).

3.3.4 Extended producer responsibility

Regulators should not be solely responsible for guiding the effective environmental deposition of PPCPs. A cohesive and scientifically sound set of guiding principles could be designed and adopted by the industries involved in the design, distribution, manufacturing, packaging, and purveyance of PPCPs. This can influence or guide consumers to take action for better environmental management of PPCPs (Daughton, 2003). An integrated system-wide approach should be designed to reduce the release of PPCPs to the environment, such as "cradle-to-cradle" design and stewardship

programs. This approach will include designing products for the environment, its life cycle assessment, extended product responsibility (EPR), eco-effectiveness, programs for taking back of the product, zero waste, and zero emissions (Daughton, 2003; Subramanian, Gupta & Talbot, 2009). For example, emissions of PPCPs posing an unacceptable risk to the environment can be reduced by a) replacing them with environmentally benign compounds; b) developing better drug delivery systems, where smaller doses are emphasized; and, c) improving and reducing the size of packaging to increase the shelf life and reduce the amount of product that gets expired or discarded as unused (Boxall et al., 2012). The release of harmful PPCPs into the environment can also be reduced by adding information about the environmental impacts of a PPCP to its packaging label (Rubik, 1995). For example, Sweden has discussed introducing an environmental label for pharmaceuticals, in cooperation with the chemical industry. This would enable physicians and patients to select the most environmentally friendly pharmaceuticals for a particular course of treatment (Wennmalm & Gunnarsson, 2009). Overall, management actions along with a greater emphasis on toxicity studies of PPCPs can contribute to efforts to reduce or minimize their introduction into aquatic environments.

3.4 Concluding remarks

The occurrence of PPCPs in aquatic environments is adversely affecting aquatic life, which is of serious ecological concern. Water pollution by PPCPs has emerged in the last two decades and will increase in the future with the rising global population and increasingly extensive use of PPCPs. Therefore, there is an urgent need to manage this human-ecological problem. This can be done by conducting more research on the aquatic toxicity of PPCPs to understand its extent and magnitude and by taking appropriate

management actions to reduce or minimize the levels of PPCPs in the aquatic environment.

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APPENDIX A

Table A.1. List of PPCPs in aquatic ecosystems addressed in five key studies with the 12 priority PPCPs selected for review (highlighted). The priority PPCPs were selected from three of the studies (Ebele et al., 2017; Meador et al., 2017; Zhang et al., 2017) based on relative risk of toxicity to non-target and freshwater aquatic organisms and adverse effects in fish. Although not addressed in this review, many of the priority PPCPs are also persistent in the aquatic environment, bioaccumulate in non-target aquatic organisms, impact urban receiving waters, or occur in wastewater treatment processes (highlighted) (Ebele et al., 2017; Ellis, 2008; Guerra et al., 2014). PPCPs are listed alphabetically.

Ebele et al., 2017			Meador et al., 2017	Zhang et al., 2017	Ellis, 2008	Guerra et al., 2014
PPCPs persistent in the aquatic environment	**PPCPs bioaccumulating in non-target aquatic organisms**	**PPCPs toxic to non-target aquatic organisms**	**PPCPs causing potential adverse effects in marine fish**	**PPCPs causing risk to freshwater aquatic organisms**	**Priority PPCPs impacting urban receiving waters**	**PPCPs occurring in wastewater treatment processes**
Pharmaceuticals						
Acetaminophen	Amitriptyline	Ampicillin	Alprazolam	Atenolol	Acetylsalicylic acid	Acetaminophen
Atenolol	Amlodipine	17 beta-estradiol	Amlodipine	Erythromycin	Atenolol	Azithromycin
Carbamazepine	Amphetamine	Carbamazepine	Amphetamine	Carbamazepine	Acetaminophen	Betamethasone
Clofibric acid	Atenolol	Ciprofloxacin	Azithromycin	Metoprolol	Bezafibrate	Carbadox
Diazepam	Azithromycin	Cisplantin	Caffeine	Naproxen	Carbamazepine	Cefotaxime
Diclofenac	Betamethasone	Cytarabine	Diphenhydramine	Norfloxacin	Clofibric acid	Chlortetracycline
Dilantin	Carbamazepine	Diclofenac	Diltiazem	Ofloxacin	Chloramphenicol	Clarithromycin
Erythromycin	Cefotaxime	Erythromycin	Desmethyldiltiazem	Sulfamethoxazole	Diazepam	Ciprofloxacin
Galaxolide	Citalopram	Fluoxetine	Fluoxetine		Diclofenac	Clinafloxacin
Gemfibrozil	Clarithromycin	Fluvoxamine	Fluocinonide		Erythromycin	Cloxacillin
Genistein	Clotrimazole	5-Fluorouracil	Metformin		Etofibrate	Codeine
2-hyroxyibuprofen	Cocaine	Gemfibrozil	Norverapamil		Fluoxetine	Demeclocycline
Ibuprofen	Codeine	Ibuprofen	Norfluoxetine		Fenofibric acid	Doxycycline
Iopromide	Diltiazem	levofloxacin	Ranitidine		Flucloxacillin	Erythromycin
Ivermectin	1,7-Dimethylxanthine	Metoprolol	Sertraline		Gemfibrozil	Enrofloxacin
Meprobamate	Diphenhydramine	Naproxen			Ibuprofen	Flumequine

Oxazepam	Enrofloxacin	Ofloxacin			Indometacine	Fluocinonide
Roxithromycin	Erythromycin	Oxolinic acid			Ketoprofen	2-Hydroxy-ibuprofen
Salicylic acid	Fluoxetine	Oxytetracycline			Lincomycin	Hydrocodone
Sulfamethoxazole	Gemfibrozil	Propranolol			Mesalazine	Ibuprofen
	Glyburide	Sertraline			Metformin	Lomefloxacin
	Hydrocortisone	Sulfamethoxazole			Naproxen	Lincomycin
	10-hydroxy-amitriptyline	Sulfadimethoxine			Primidone	Miconazole
	Ibuprofen	Tetracycline			Salbutamol	Minocycline
	Iopamidol	Trimethoprim			Sulfamethaxole	Naproxen
	Metformin				Sulfasalazine	Norfloxacin
	Miconazole				Trimethoprim	Methylprednisolone
	Minocycline					Ofloxacin
	Naproxen					Oxycodone
	N-Desmethyldiltiazem					Ormetoprim
	Norfluoxetine					Oxacillin
	Norverapamil					Oxolinic acid
	Oxazepam					Oxytetracycline
	Oxolinic Acid					Penicillin G
	Oxycodone					Penicillin V
	Paroxetine					Prednisolone
	Propranolol					Roxithromycin
	Sarafloxacin					Sarafloxacin
	Sertraline					Sulfachloropyridazine
	Theophylline					Sulfadiazine
	Venlafaxine					Sulfadimethoxine
	Verapamil					Sulfamerazine
	Warfarin					Sulfamethazine
						Sulfamethizole
						Sulfamethoxazole

						Sulfanilamide
						Sulfathiazole
						Tetracycline
						Thiabendazole
						Trimethoprim
						Virginiamycin
Personal care products						
N,N-Diethyl-meta-toluamide (DEET)	Bisphenol A	Bisphenol A	N,N-Diethyl-meta-toluamide (DEET)	Bisphenol A	Benzophenone	Triclocarban
Nonylphenol	Triclocarban	Nonylphenol	Triclocarban	Diethylhexyl phthalate	Chlorophene	Triclosan
Triclosan	Methyl-triclosan	Triclosan	Triclosan	Linear alkylbenzene sulfonate	Methyl benzylidene camphor	
	N,N-Diethyl-meta-toluamide (DEET)			Nonylphenol	Musks	
	Nonylphenol				N,N-Diethyl-meta-toluamide (DEET)	
	Triclosan				Phthalates	
					Triclosan	

APPENDIX B

References for Tables 2.4 and 2.5

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