

REVIEW

Pharmaceuticals and personal care products (PPCPs) are ecological disrupting compounds (EcoDC)

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Pharmaceuticals and personal care products (PPCPs) are ubiquitous in freshwater ecosystems worldwide and are recognized as contaminants of concern. Currently, contaminants of concern are classified for their persistence, bioaccumulation, and toxicity (PBT criteria). PPCPs are not classified as persistent organic pollutants (POPs), although some PPCPs share characteristics similar to POPs. For example, PPCPs are known to be pseudopersistent due to constant discharge into the environment, often at low concentrations. At commonly reported environmental concentrations, PPCPs are rarely toxic, but the ability of these compounds to disrupt ecological processes and functions in freshwater ecosystems is often overlooked. Herein we briefly summarize recent studies highlighting the potential ecological effects of PPCPs, including effects on key ecological processes (e.g. primary productivity and community respiration), and we propose that appropriate screening for harmful effects of PPCPs in surface waters should be expanded to include Ecologically Disrupting Compounds (EcoDC) in addition to the established PBT criteria.

Keywords: PPCPs; ecological processes; disruption; pharmaceuticals; sub-lethal; EcoDC

Introduction

Pharmaceuticals and personal care products (PPCPs) are biologically active compounds that are recognized as environmental contaminants of global concern due to their presence in ecosystems throughout the world (Monteiro and Boxall, 2010) and more recently as agents of global change (Bernhardt et al., 2017). PPCPs can enter the environment through multiple pathways, including both point and non-point sources, and are commonly detected in surface waters at low concentrations (ng to $\mu\text{g L}^{-1}$) (Daughton and Ternes, 1999). As the global human population and percentage of the population living in high-density urban areas continue to increase, PPCP contamination of ecosystems is expected to increase substantially both in the number of contaminated ecosystems, and in the typical PPCP concentration found in the environment (Weber et al., 2015). Additionally, it is likely that the contribution of increased water usage to global water shortages will

further exacerbate concentrations of PPCPs (Klaminder et al., 2015; Petrovic et al., 2011).

Relative to other types of organic chemicals, e.g. polychlorinated biphenyls (PCBs), questions surrounding the biological impacts of PPCPs remain largely unanswered (Monteiro and Boxall, 2010). Currently, organic contaminants are screened and classified for potential harmful effects using PBT (persistence, bioaccumulation, and toxicity) criteria (EPA, 2012; Klečka et al., 2009; Stempel et al., 2012). In contrast to the US EPA approach, the European Union Water Framework Directive has identified a list of priority substances based upon similar criteria to the EPA, but using precautionary principles, this list is to be updated every 4 years to include pseudopersistent PPCPs (Ellis, 2006). Although many PPCPs have a limited lifespan in the environment, PPCPs are often classified as pseudopersistent based on the continual addition of these compounds to the environment (Daughton and Ternes, 1999). Furthermore, our knowledge of the persistence of PPCPs in the environment is often based on laboratory studies, which can underestimate persistence for certain compounds (Klaminder et al., 2015). A review by Daughton and Ternes (1999) highlighted the need to study the environmental fate of PPCPs in a similar fashion to which persistent organic pollutants (POPs) such as some pesticides and other organic contaminants have been studied. Despite this call for more research on the environmental fate of PPCPs, we still lack a solid understanding of the fate and bioaccumulation of PPCPs in the environment (e.g. Walters et al., 2016) and of the effects

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of PPCPs on ecosystem function. This knowledge gap is particularly noteworthy, as synthetic chemicals similar to PPCPs have recently received attention and are also not well studied in ecological and environmental research (Bernhardt et al., 2017).

In 1999 the United States Geological Survey (USGS) undertook a national survey to quantify the presence of organic contaminants, including PPCPs, in US surface waters. The results of this study indicated that organic contaminants were detected in 80% of streams sampled across 30 US states and that detection of multiple contaminants in a single sample was common (Kolpin et al., 2002). Similar results were observed in a recent survey conducted by the USGS, where 84 PPCPs were detected in 38 US streams (Bradley et al., 2017). The landmark study by Kolpin et al. (2002), emulated by numerous additional studies, highlighted the many PPCPs in surface waters throughout the world (e.g. Stewart et al., 2014; Kasprzyk-Hordén et al., 2008). A majority of these compounds, largely understudied, are currently unregulated or have been determined to be low risk due to low environmental concentrations, possibly because the perceived social benefit outweighs associated environmental risks. Much of the research and regulatory requirements exploring the effects of these compounds have used traditional toxicity tests (e.g. the concentration required for PPCPs to cause 50% mortality (LC50s) in model organisms, or the predicted no effect concentration (PNEC) of a compound). These conventional toxicity tests included in the PBT criteria show that PPCPs have the capacity to be toxic at high concentrations (exceeding human therapeutic doses) and typically conclude that PPCPs in the environment are not hazardous due to low environmental concentrations, despite often only testing effects on model organisms (e.g. the common green alga *Scenedesmus*). More simply, the LC50s of these compounds are much higher than concentrations detected in the environment. Therefore, pharmaceuticals are usually classified as non-toxic, although a notable publicized exception was the widespread mortality of old world vultures consuming dead livestock that had been previously treated with a veterinary anti-inflammatory drug (Oaks et al., 2004).

Despite the general lack of toxic effects at environmentally relevant concentrations, PPCPs are capable of causing various sub-lethal ecological effects on many components of aquatic ecosystems, thus emphasis should be placed on evaluating over all ecosystem effects of PPCPs. The US Food and Drug Administration (FDA) only requires an environmental assessment report for new drug applications if the concentration reaching surface waters is $>1 \mu\text{g/L}$ (FDA, 1998). However, pharmaceuticals are designed to be effective and used at low therapeutic doses, potentially causing sub-lethal effects in natural environments. Therefore, we contend that the effects of these compounds cannot be readily ascertained with traditional toxicity testing alone and that the current emphasis on single organismal lethality could lead the scientific and regulatory community to underestimate the potential risks of PPCPs to aquatic ecosystems.

Known ecological disrupting effects of PPCPs

Recent research investigating sub-lethal ecological effects of PPCPs has demonstrated that environmentally relevant concentrations of these compounds may alter ecological interactions and processes (**Table 1**). PPCPs can also alter relationships among organisms. For example, a common antidepressant, oxazepam, alters the feeding behavior of European perch (Brodin et al., 2013; Brodin et al., 2014), and tadpoles (*Bufo arabicus*) were more susceptible to predation from predatory dragonfly larvae (*Anax imperator*) when exposed to low concentrations of the selective serotonin reuptake inhibitor (SSRI) fluoxetine ($3 \mu\text{g/L}$) (Barry, 2014). PPCPs can also promote changes in ecosystem structure and function, including biofilm primary production, respiration and community structure, biogeochemical processes, and invertebrate growth and population dynamics. Microbial respiration was suppressed when exposed to common pharmaceuticals including caffeine (53%), ciprofloxacin (91%), cimetidine (51%) and diphenhydramine (63%) which also almost completely suppressed photosynthesis (99%) (Rosi-Marshall et al., 2013). Similarly, biofilm primary production was suppressed by over 88% when exposed to the illicit drug amphetamine (Lee et al., 2016). In addition, fluoxetine and citalopram, which are commonly used antidepressants, reduced algal production by 29% (Richmond et al., 2016). Altering one or several ecosystem processes can irreparably disrupt ecological systems. For example decreases in primary production can reduce the organic matter available to higher trophic levels, thereby altering food web dynamics (Polis and Strong, 1996).

Similar to functional responses, PPCPs can induce alterations to bacterial and diatom communities and can select for antimicrobial resistance both in laboratory and field settings. Diphenhydramine exposure altered bacterial composition on novel test substrates in streams by increasing the relative abundance of a common biofilm producing bacterium, *Pseudomonas*, while causing relative decreases in *Flavobacterium* sp. (Rosi-Marshall et al., 2013). Likewise, artificial streams amended with $1 \mu\text{g/L}$ amphetamine significantly altered diatom communities (Lee et al., 2016), and a combination of 9 PPCPs (total $5 \mu\text{g/L}$) and altered flow regimes reduced biofilm taxonomic richness and biomass, while also changing the structure of the bacterial community (Corcoll et al., 2015). Furthermore, concentrations of triclosan, a common antimicrobial, have been found to alter the structure of bacterial communities and increase antimicrobial resistant bacteria (Drury et al., 2013b; Proia et al., 2011), both in situ and in artificial streams amended with triclosan. In addition, streams that receive wastewater effluent displayed significantly reduced abundance and diversity of benthic bacterial communities (Drury et al., 2013a), although this may also have been as a result of other contaminants found in wastewater besides PPCPs.

Pharmaceuticals can also disrupt and alter processes within aquatic invertebrate communities, and these disruptions or alterations can in turn disrupt other ecosystem functions. For example, aquatic insect metamorphosis and emergence occurred sooner and at

Table 1: Examples of relevant studies documenting ecological disruption resulting from low-dose, sub-lethal environmental concentrations of PPCPs. DOI: <https://doi.org/10.1525/elementa.252.t1>

PPCP	Test biota	Concentration ($\mu\text{g/L}^{-1}$)	Effect summary	Citation
Amphetamine (illicit drug)	Stream benthic communities	1	Suppression of gross primary production on autotrophic biofilms, compositional shift of bacterial and biofilm communities, increased dipteran (stream insect) emergence	(Lee et al., 2016)
Caffeine (stimulant), acetaminophen (pain reliever), diclofenac (anti-inflammatory)	Protozoa, micrometazoa and algae	5	Increased abundance of organisms and feeding activity (direct), decreased biofilm (algal) biomass (indirect)	(Lawrence et al., 2012)
Cimetidine (antihistamine)	Invertebrates (<i>Gammarus fasciatus</i> and <i>Psephenus herricki</i>)	0.07–70	Reduced growth and biomass of <i>G. fasciatus</i> , low survivorship of <i>P. herricki</i> when exposed to high concentrations	(Hoppe et al., 2012)
Diuron (herbicide), triclosan (antimicrobial)	River biofilm communities	15–60	Biofilm recovery after exposure to short term pulses of triclosan and diuron	(Proia et al., 2011)
Fluoxetine (antidepressant), citalopram (antidepressant)	Algal and invertebrate benthic communities	20	Suppression of primary productivity and community respiration on biofilms (algae). Increased stream insect emergence	(Richmond et al., 2016)
Oxazepam (antidepressant)	European Perch (<i>Perca fluviatilis</i>)	1.8	Increased feeding rates and locomotor activity (direct); implications for prey populations (indirect)	(Brodin et al., 2013)
Oxazepam (antidepressant)	European Perch (<i>Perca fluviatilis</i>), Mayfly (<i>Coenagrion hastulatum</i>)	2	Increased predator activity of perch, no behavioral effects on mayflies (direct). Increased bioaccumulation via consumption of exposed prey (indirect)	(Brodin et al., 2014)
Triclosan (anti-microbial)	Benthic bacterial communities	1–107 ng/g sediment (field sites) 17.3 $\mu\text{g/g}$ (max concentration, mesocosm)	Field and laboratory experiment. Correlation between sediment triclosan concentration and abundance of triclosan resistant bacteria at field sites. Increased abundance of triclosan resistant bacteria in mesocosms	(Drury et al., 2013b)
Triclosan (antimicrobial)	Stream benthic communities	0.1–10	Increase in abundance of triclosan resistant bacteria and stimulation of periphyton growth	(Nietch et al., 2013)
Wastewater treatment plant (WWTP) effluent	Benthic bacterial communities	N/A	Field experiment. Changes in bacterial abundance and community composition above and below WWTPs	(Drury et al., 2013a)

a greater rate when insect larvae (Diptera) were exposed to 20 µg/L of fluoxetine and citalopram (Richmond et al., 2016), and cumulative insect emergence increased by up to 89% when exposed to amphetamine (Lee et al., 2016). Cimetidine, a common antihistamine, reduced *Gammarus* biomass when exposed to low concentrations (0.07–70 µg/L) (Hoppe et al., 2012) and exposure to low concentrations of an antibiotic mixture (2 µg/L) led to shifts in leaf microbial communities, resulting in increased amphipod (*Gammarus*) body mass (Bundschuh et al., 2017). Changes in animal biomass, particularly for primary consumers near the base of a food web, can affect population and community dynamics within aquatic ecosystems, whereas altered phenology and mass fluxes of aquatic insect emergence have energetic implications for linked aquatic and terrestrial food webs (Baxter et al., 2005), and can alter riparian community structure (Kalcounis-Rueppell et al., 2007).

It is also worth noting that ecological disruption by PPCPs can be direct or indirect, analogous to other traditional drivers of ecological interactions (McQueen et al., 1986; Polis et al., 1997; Wootton, 1994). For example, as mentioned earlier, European Perch (*Perca fluviatilis*) exposed to low concentrations (1.8 µg/L) of oxazepam, a common psychoactive drug, accumulated the pharmaceutical in their tissues and exhibited altered behavior, including increased feeding rate (direct effect; Brodin et al., 2013). An increase in perch feeding rate could affect prey populations (indirect effect), even if the prey species was not directly affected by the drug exposure (Brodin et al., 2014). Similarly, caffeine stimulates the numbers and grazing activity of microscopic animals such as nematodes and rotifers (direct effect), which results in decreased biomass of algae and bacteria in aquatic biofilms (indirect effect; Lawrence et al., 2012). These indirect ecological effects demonstrate that a specific biochemical interaction is not always necessary for a pharmaceutical to act as an ecological disruptor and affect organisms, community dynamics, or ecological processes (Table 1). Moreover, the ecological effects of single PPCP compound exposure may be incalculably increased by simultaneous exposure to the wide range of PPCP compounds commonly detected in surface waters (Bradley et al., 2017). Many of these effects remain largely unknown or undetected, in part because they may be subtle and difficult to measure. Based upon this recent research, we conclude that PPCPs can have profound ecological impacts capable of disrupting ecological dynamics. Therefore, we propose that appropriate screening for harmful effects of PPCPs in surface waters should be expanded to include ecological disruption, highlighting PPCPs as Ecological Disrupting Compounds (EcoDC), in addition to the established PBT criteria.

Our concept of EcoDCs (Figure 1A) is analogous to endocrine disrupting compounds (EDCs), which are generally non-toxic but can alter the endocrinology of organisms at environmentally relevant concentrations (Clotfelter et al., 2004). The presence of EDCs in surface waters has been well documented over the last two decades, and a growing body of literature has examined the potential for EDCs to cause non-lethal effects on aquatic biota at

low concentrations, particularly changes in behavior and sexual reproduction of organisms (Clotfelter et al., 2004; Colborn et al., 1993). In 1998, the EPA Endocrine Disruptor Screening and Testing Advisory Committee was formed to make federal recommendations regarding adverse effects of EDCs found in the environment (EPA, 1998). After the recommendations of the committee were published, the presence of EDCs in the environment and their ability to cause non-lethal effects has received considerable attention.

Research priorities and implications for resource and policy managers

Despite the need for a better understanding of the environmental fate of PPCPs (Daughton and Ternes, 1999) and a growing body of evidence documenting sub-lethal and ecosystem-level effects, studies on toxicity of PPCPs vastly outnumber those on ecosystem disruption. Based on a literature search using Web of Science, >90% of scientific articles studying the effects of PPCPs have quantified lethal endpoints (Figure 1B). Of the articles that measured endpoints associated with ecological disruption at environmentally relevant PPCP concentrations, over half (55%) focused on behavioral alterations of a target organism, rather than quantifying changes in ecological functions and community dynamics or indirect effects (Figure 1C). The apparent lack of contaminant studies focusing on ecological endpoints can be at least partially attributed to the limited funding for research on PPCPs by major funding agents such as the National Science Foundation (Bernhardt et al., 2017). This funding gap, coupled with the focus on traditional toxicity testing, results in a loss of cohesion between ecotoxicological and ecological disciplines and thus long term, subtle, ecological disruption endpoints are often overlooked.

The use of PPCPs will likely continue to increase throughout the world as the proportion of the global population with access to treatment increases, so the release of PPCPs to surface waters is likely to increase rather than abate in the near future (Schroder et al., 2016). In addition, increased water-use efficiency will likely contribute to an increase of PPCP concentrations in the environment (Klaminder et al., 2015). Although the toxic effects of many PPCPs are limited to concentrations much higher than typically detected in the environment, there is growing scientific evidence that these compounds can act as Ecological Disrupting Compounds with heretofore unknown and unpredictable long-term effects. Current chemical and contaminant management practices do not appropriately address these issues and we argue that an additional standardized criterion should be established for risk assessments of these biologically active compounds that includes consideration of their potential to disrupt ecological processes across multiple components of an aquatic ecosystem, and that this criterion recognizes this potential even at low (<1 µg/L) concentrations. Beyond the scope of the current review, efforts to develop standardized protocols to quantify sub-lethal effects as well as community- and ecosystem-level effects are needed. Although difficult to standardize due to the myriad

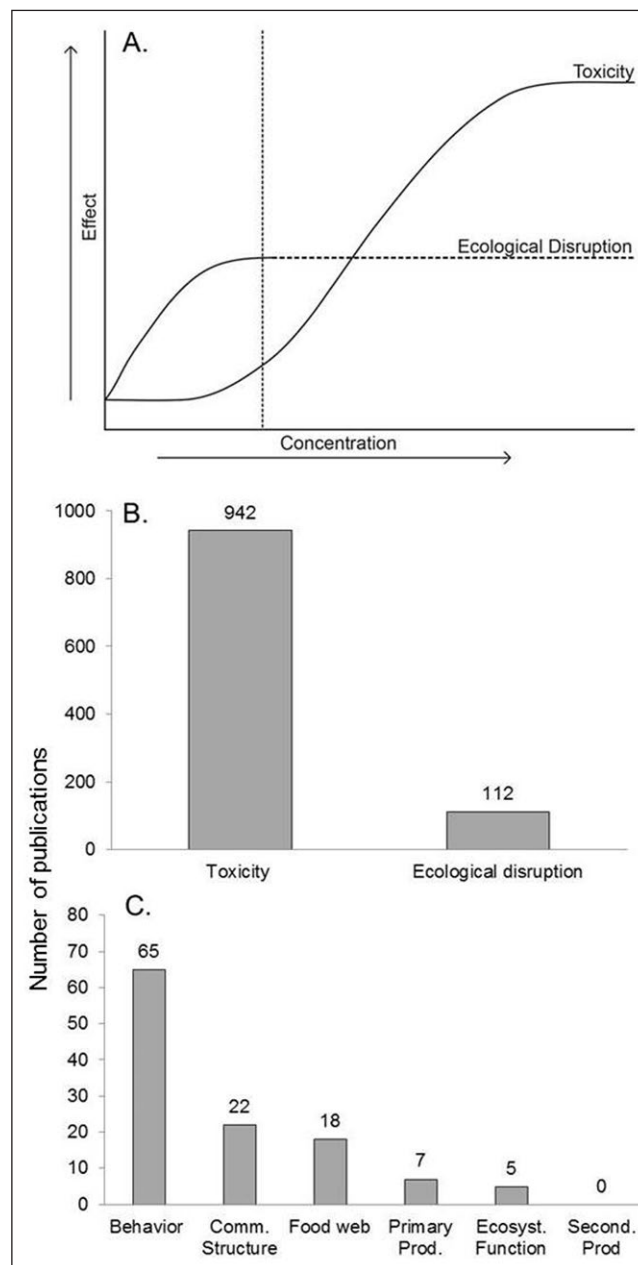


Figure 1: PPCPs as EcoDCs influence aquatic ecosystem function and biota. A) Conceptual figure demonstrating the potential non-lethal effects of EcoDCs at low concentrations on aquatic biota and ecosystem function, in contrast to toxic effects observed at high concentrations. The dashed horizontal line at the end of this curve represents uncertainty at high PPCP concentrations. The dashed vertical line indicated where lethality is becoming increasingly important relative to ecosystem disruption. **B)** Number of publications indexed in Web of Science measuring toxic endpoints (including LC50 and EC50 toxicity testing) versus those measuring non-lethal, ecological disruption (EcoD) endpoints at environmentally relevant concentrations. **C)** Number of publications in Web of Science demonstrating various endpoints related to ecosystem disruption associated with environmentally relevant concentrations of PPCPs. Details of literature search are available in supplementary material. DOI: <https://doi.org/10.1525/elementa.252.f1>

environmental conditions that could affect PPCP EcoDC, future research and protocol development in this area are vital. Building off of this argument, we recommend adding EcoDC to the PBT toxicology criteria for this group of compounds. In support of this recommendation we have provided examples to demonstrate that pharmaceuticals have biological consequences at low, non-toxic concentrations. These concentrations seldom cause mortality, but

have the ability to alter life histories and behaviors, and change processes and community structure within aquatic systems. We further suggest that future research consider testing for ecological disruption and focus on the potential effects of pharmaceuticals on the ecology and biology at all levels of aquatic ecosystems to better understand the long-term consequences of environmental exposures to these organic chemicals.

Supplemental File

The supplemental file for this article can be found as follows:

- **Text S1.** Search terms in Web of Science for Figure 1B and C. DOI: <https://doi.org/10.1525/elementa.252.s1>

Acknowledgements

We thank Dr. Emily Bernhardt for providing helpful comments on an earlier draft of the manuscript. This research was subjected to USGS review and approved for publication. Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the U.S. Government.

Funding information

We acknowledge that funding for Erinn Richmond was provided by Monash University, Faculty of Science Dean's Postgraduate award.

Competing interests

The authors have no competing interests to declare.

Author contributions

- Contributed to conception and design: EKR, MRG, JJK, AJR, EJR, DMW
- Contributed to acquisition of data: EKR, EJR, DMW
- Contributed to analysis and interpretation of data: EKR, EJR, DMW
- Drafted and/or revised the article: EKR, MRG, JJK, AJR, EJR, DMW
- Approved the submitted version for publication: EKR, MRG, JJK, AJR, EJR, DMW

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How to cite this article: Richmond, EK, Grace, MR, Kelly, JJ, Reisinger, AJ, Rosi, EJ and Walters, DM 2017 Pharmaceuticals and personal care products (PPCPs) are ecological disrupting compounds (EcoDC). *Elem Sci Anth*, 5: 66. DOI: <https://doi.org/10.1525/elementa.252>

Domain Editor-in-Chief: Donald R. Zak, University of Michigan, US

Associate Editor: Julian D. Olden, University of Washington, US

Knowledge Domain: Ecology

Submitted: 18 May 2017 **Accepted:** 25 September 2017 **Published:** 13 November 2017

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