

# Does Environmental Exposure to Pharmaceutical and Personal Care Product Residues Result in the Selection of Antimicrobial-Resistant Microorganisms, and is this Important in Terms of Human Health Outcomes?

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**Abstract:** The environment plays a critical role in the development, dissemination, and transmission of antimicrobial resistance (AMR). Pharmaceuticals and personal care products (PPCPs) enter the environment through direct application to the environment and through anthropogenic pollution. Although there is a growing body of evidence defining minimal selective concentrations (MSCs) of antibiotics and the role antibiotics play in horizontal gene transfer (HGT), there is limited evidence on the role of non-antibiotic PPCPs. Existing data show associations with the development of resistance or effects on bacterial growth rather than calculating selective endpoints. Research has focused on laboratory-based systems rather than in situ experiments, although PPCP concentrations found throughout wastewater, natural water, and soil environments are often within the range of laboratory-derived MSCs and at concentrations shown to promote HGT. Increased selection and HGT of AMR by PPCPs will result in an increase in total AMR abundance in the environment, increasing the risk of exposure and potential transmission of environmental AMR to humans. There is some evidence to suggest that humans can acquire resistance from environmental settings, with water environments being the most frequently studied. However, because this is currently limited, we recommend that more evidence be gathered to understand the risk the environment plays in regard to human health. In addition, we recommend that future research efforts focus on MSC-based experiments for non-antibiotic PPCPs, particularly in situ, and investigate the effect of PPCP mixtures on AMR. *Environ Toxicol Chem* 2022;00:1–14. © 2022 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

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## INTRODUCTION

Antimicrobial resistance (AMR) is a global health crisis, with estimates suggesting that 1.27 million deaths globally in 2019 were attributable to antibacterial resistance (Antimicrobial Resistance Collaborators, 2022). Predictions have

suggested that this could rise to 10 million deaths annually by 2050 if no steps are taken to address the issue (O'Neill, 2014). Many studies regard the environment as a source of AMR, clinically relevant or otherwise (Pärnänen et al., 2016; Perry & Wright, 2013); and increasing evidence supports the view that the environment plays an important role in the development, dissemination, and transmission of AMR (Singer et al., 2016).

Many sources and dissemination routes of pharmaceuticals and personal care products (PPCPs) into the environment exist (Figure 1). Pharmaceuticals and personal care products, such as prescription and non-prescription drugs, illicit drugs, cosmetics, disinfectants, detergents, and food preservatives, enter the environment through anthropogenic pollution sources (e.g., biocides released from laundry detergent [Dey et al.,

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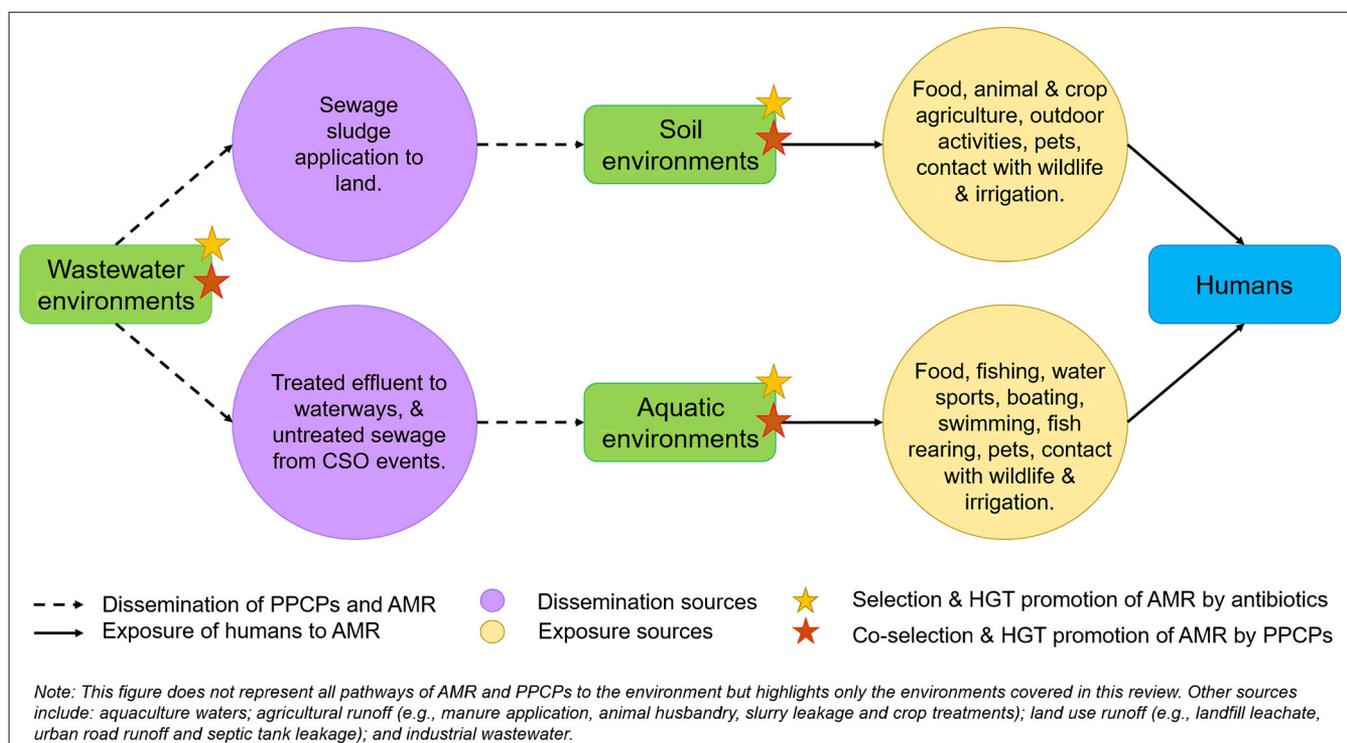
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**FIGURE 1:** Systems map showing pharmaceutical and personal care product (PPCP) and antimicrobial resistance (AMR) dissemination routes through the environment covered in the present review, from wastewater environments to the natural environment. Environments where selection (by antibiotics) and co-selection (by non-antibiotic PPCPs) may occur are indicated. Exposure sources and routes of AMR to humans that may result in a human health outcome are also shown. The figure does not represent all anthropogenic sources of AMR or PPCPs into the natural environment but provides a summary of those discussed in the present review. CSO = combined sewage overflow; HGT = horizontal gene transfer.

2019] or pharmaceuticals released from drug manufacturing effluent [Kümmerer, 2009]). Inappropriate disposal practices, such as discarding licit and illicit drugs into household waste, can also contribute (Dey et al., 2019).

In the environment, PPCPs potentially increase AMR levels through selection or co-selection. Selection occurs when a chemical exerts direct selective pressure on a resistance gene or mutation that confers resistance against that chemical. Co-selection occurs when a non-antimicrobial chemical exerts an indirect selection pressure on an antibiotic resistance gene (ARG). This occurs via co-location of genes conferring resistance to different compounds on a plasmid or other genetic element (co-resistance; Baker-Austin et al., 2006) or when a single resistance mechanism provides resistance to multiple compounds (cross-resistance; e.g., efflux pumps; Chapman, 2003).

In 2012, the top 20 questions concerning the hazards, exposure assessment, and environmental and health risks of PPCPs in the natural environment were derived by a set of prominent experts in the field at a technical workshop hosted by the Society of Environmental Toxicology and Chemistry's Pharmaceutical Advisory Group (Boxall et al., 2012). The question posed in the title of the present review—"Does environmental exposure to PPCP residues result in the selection of antimicrobial resistant microorganisms, and is this important in terms of human health outcomes?"—was ranked third most important out of the final 20 key questions decided by workshop participants. On the tenth anniversary of the Boxall et al. publication,

we hope to address this question by reviewing whether PPCP residues in the environment select or co-select for AMR and discuss the relevant importance to human health outcomes.

## LABORATORY-BASED STUDIES INVESTIGATING SELECTION AND CO-SELECTION OF AMR

### Selection

A number of laboratory studies have investigated whether subinhibitory (environmentally relevant) concentrations of antibiotics select for AMR. The lowest-observable-effect concentration (LOEC) that selection occurs at is often called the minimal selective concentration (MSC), and these terms are often used interchangeably. The MS/LOECs can inform discharge limits of antibiotics and can be used in risk assessments to understand the hazard posed by measured environmental concentrations (MECs). The highest concentration tested directly below the MSC/LOEC is termed the no-observable-effect concentration, on which assessment factors can be applied to calculate a predicted-no-effect concentration (PNEC; or PNEC for resistance [PNEC<sub>R</sub>] in the case of AMR). By dividing MECs by PNEC values, a risk quotient can be calculated, where risk quotients >1 indicate high-risk environments (European Medicines Agency, 2006; Murray et al., 2021). Risk of selection is likely greater than single-chemical risk quotient values when we consider the total mixed chemical load in the environment.

The main experimental methods used to derive MSCs have been single-species competition assays. For single-species competition assays, selection coefficients (changes in the ratio of resistant to susceptible bacteria over time) were calculated to estimate MSCs (Gullberg et al., 2011, 2014; Kraupner et al., 2020; Liu et al., 2011; Vos et al., 2020). Competition assays have also been used to show that mixed communities require higher antibiotic concentrations to cause selection (Klümper et al., 2019).

Other studies have used complex, environmental communities that resemble natural environments to define MSCs. These often involve liquid microcosm experiments or biofilms inoculated with sewage bacterial communities that are evolved in the presence of antibiotics. Increases in resistance can be measured phenotypically (e.g., agar plating) or genotypically, with changes in gene prevalence quantitated with quantitative polymerase chain reaction (qPCR) or metagenomic sequencing. The three key approaches taken are as follows. 1) Microcosm evolution experiments using qPCR to measure ARGs (Kraupner et al., 2018; Murray et al., 2018, 2020; Stanton et al., 2020), sequencing to measure ARGs (Murray et al., 2018; Stanton et al., 2020), and/or plating to measure phenotypic resistance (Kraupner et al., 2020; Stanton et al., 2020). 2) A validated growth rate assay using growth rate as a proxy for selection (the Selection Endpoints in Communities of Bacteria assay; Murray et al., 2020). 3) Biofilms used in flow-through experiments exposing wastewater to antibiotics using qPCR to measure ARGs (Lundström et al., 2016), sequencing to measure ARGs (Kraupner et al., 2018, 2020; Lundström et al., 2016), and plating to measure phenotypic resistance (Lundström et al., 2016).

A table of available MSCs/LOECs has been collated by Murray et al. (2021), detailing test antibiotics, methods, analyses, and the MSCs/LOECs/PNECs found. We have provided a condensed version of this (Table 1), with updated experimentally derived MSC and LOEC values that were published after Murray et al. (2021). In addition to experimentally derived endpoints, PNEC<sub>RS</sub> have been modelled for 111 antimicrobials and 11 antibiotic combinations. These PNEC<sub>RS</sub> were based on minimum inhibitory concentration (MIC) values from the EUCAST database (European Committee on Antimicrobial Susceptibility Testing, 2022). The lowest 1% of observed MICs was identified and a 10-fold assessment factor applied. Values of PNEC<sub>R</sub> ranged from 0.008 (itraconazole) to 64 µg/L (nitrofurantoin; Bengtsson-Palme & Larsson, 2016).

Evidence suggests that antibiotic transformation products (Fatta-Kassinos et al., 2011) and enantiomeric antibiotics (Elder et al., 2020) could also select for AMR. In addition, sub-MSC concentrations have been shown to increase persistence of ARGs within bacteria communities (Kraupner et al., 2020; Larsson & Flach, 2021; Stanton et al., 2020). The lowest concentration at which this occurs is termed the minimal increased persistence concentration (Stanton et al., 2020).

The laboratory work investigating antimicrobials selecting for AMR has largely focused solely on antibiotics selecting for antibiotic resistance. However, Khan et al. (2017) determined multiple MSCs for the disinfectants chlorine and monochloramine using single-species competition assays. In addition, a

recent review compared laboratory methodologies used to define MSCs for antibiotics and discussed the strengths and weaknesses of these in relation to their use in defining antifungal MSCs for antifungal resistance (Stevenson et al., 2022).

## Co-selection

Many compounds can potentially co-select for resistance, including PPCPs and non-PPCPs, such as metals. Non-antibiotic PPCPs potentially co-select for AMR, although research remains limited. Research often focuses on co-selection by disinfectants, insect repellents, and preservatives in personal care products (PCPs). Benzalkonium chloride (BAC) is a quaternary ammonium compound (QAC) and disinfectant found in cosmetics, household cleaners, and washing detergents (Buffet-Bataillon et al., 2012). The QAC-resistance gene *qacEΔ1* forms part of the backbone of the genetic element Class 1 integron that carries numerous AMR gene cassettes. Thus, exposure to QACs may maintain or select for Class 1 integrons (harboring ARGs), resulting in co-selection of AMR by co-resistance (Moura et al., 2009; Partridge et al., 2009).

Several studies have investigated the co-selective potential of BAC. *Listeria monocytogenes* evolved higher ciprofloxacin MICs when experimentally exposed to BAC, with environmental strains having higher basal QAC MICs than those isolated from food (Guérin et al., 2021). Studies on Gram-positive species found that BAC exposure can decrease antibiotic susceptibility (Kampf, 2019) and increase antibiotic MICs (Nordholt et al., 2021). The relevance of this to contaminated environments is questionable, given the use of single-strain experiments and inhibitory concentrations. However, increases in AMR and antibiotic tolerance have been observed in experiments using river sediment communities exposed to subinhibitory concentrations of BAC (Kim et al., 2018; Oh et al., 2013). Another study exposed *Pseudomonas aeruginosa* to increasing concentrations of BAC and found that ciprofloxacin MICs increased by 256-fold. However, a study using untreated sewage as inoculum found that BAC exposure did not enrich antimicrobial, metal, or biocide resistance genes (Murray et al., 2019).

Triclosan is a disinfectant found in PCPs, though it has now been banned in soap products in many countries (Sinicropi et al., 2022). One study evolving *Stenotrophomonas maltophilia* in the presence of triclosan found reduced susceptibility to tetracycline, chloramphenicol, and ciprofloxacin, mediated through overexpression of the multidrug efflux pump *SmeDEF* (Sanchez et al., 2005). Another study using a complex community in an anaerobic digester showed that high triclosan concentrations increased tolerance to ciprofloxacin (Carey & McNamara, 2016). Subinhibitory concentrations of triclosan also decrease susceptibility of *Escherichia coli* to ciprofloxacin, penicillin, kanamycin, and gentamicin, although penicillin tolerance reverted to wild-type levels after 20 generations with no triclosan exposure (Li et al., 2019). *Salmonella enterica* serovar Typhimurium strains exposed to increasing triclosan concentrations showed decreased susceptibility to chloramphenicol, tetracycline, and ampicillin, with overexpression of the *AcrAB* efflux pump, suggesting further co-selective

**TABLE 1:** Summary table of laboratory-derived minimal selective concentration/lowest-observable-effect concentration values

Antibiotic	Methodology	MSC/LOEC (µg/L)	Reference
Amikacin	Single-species evolution experiment	400	Sanz-García et al. (2021)
Azithromycin	qPCR of ARGs from sewage microcosm	750	Stanton et al. (2020)
	OD using SELECT assay with sewage	1000	Murray et al. (2020)
Cefapime	Isogenic competition experiment	4.74–13.61	H. Wang et al. (2022)
	qPCR of ARGs from sewage microcosm	4	Murray et al. (2018)
Cefotaxime	qPCR of ARGs from sewage microcosm	15.63	Murray et al. (2020)
	qPCR of ARGs from sewage microcosm	125	Murray et al. (2020)
Ceftazidime	Single-species evolution experiment	400	Sanz-García et al. (2021)
Ciprofloxacin	Isogenic competition experiment	0.1	Gullberg et al. (2011)
	OD using SELECT assay with sewage	0.98	Murray et al. (2020)
	qPCR of ARGs from biofilm microcosm	1	Kraupner et al. (2018)
	qPCR of ARGs from sewage microcosm	10.77	Stanton et al. (2020)
	Isogenic competition experiment	0.004	Vos et al. (2020)
	qPCR of ARGs from sewage microcosm	15.625	Stanton et al. (2020)
	Isogenic competition in mallard gut	21	Atterby et al. (2021)
	Single-species evolution experiment	5	Sanz-García et al. (2021)
	Competition experiment in a biofilm	0.96	Tang et al. (2022)
	OD using SELECT assay with sewage	250	Murray et al. (2020)
Chloramphenicol	qPCR of ARGs from sewage microcosm	500	Murray et al. (2020)
	OD using SELECT assay with sewage	5000	Murray et al. (2020)
Clarithromycin	qPCR of ARGs from sewage microcosm	750	Stanton et al. (2020)
	OD using SELECT assay with sewage	5000	Murray et al. (2020)
Erythromycin	qPCR of ARGs from sewage microcosm	514.1	Stanton et al. (2020)
	qPCR of ARGs from sewage microcosm	750	Stanton et al. (2020)
	Isogenic competition experiment	3000	Gullberg et al. (2014)
Fosfomicin	OD using SELECT assay with sewage	25 000	Murray et al. (2020)
	Isogenic competition in planktonic system	400	Hjort et al. (2022)
Gentamicin	Isogenic competition in biofilm system	1200	Hjort et al. (2022)
	OD using SELECT assay with sewage	250	Murray et al. (2020)
Imipenem	qPCR of ARGs from sewage microcosm	250	Murray et al. (2020)
	Single-species evolution experiment	250	Sanz-García et al. (2021)
Kanamycin	Isogenic competition experiment	470	Gullberg et al. (2014)
Levofloxacin	Single-species evolution experiment	80	Sanz-García et al. (2021)
Nitrofurantoin	Isogenic competition in planktonic system	400	Hjort et al. (2022)
Polymyxin B	Single-species evolution experiment	2000	Sanz-García et al. (2021)
Rifampicin	Isogenic competition in planktonic system	1100	Hjort et al. (2022)
	Isogenic competition in biofilm system	1500	Hjort et al. (2022)
Streptomycin	Isogenic competition experiment	1	Gullberg et al. (2011)
	Isogenic competition in planktonic system	300–3100	Hjort et al. (2022)
	Isogenic competition in biofilm system	2200–5900	Hjort et al. (2022)
Tetracycline	qPCR of ARGs from biofilm microcosm	1	Lundström et al. (2016)
	Single-species evolution experiment	1500	Sanz-García et al. (2021)
	Isogenic competition experiment	15	Gullberg et al. (2011)
	Isogenic competition experiment	45	Gullberg et al. (2014)
Trimethoprim	OD using SELECT assay with sewage	31.25	Murray et al. (2020)
	Isogenic competition experiment	33	Gullberg et al. (2014)
	qPCR of ARGs from sewage microcosm	62.5	Murray et al. (2020)
	Isogenic competition experiment	100	Kraupner et al. (2020)
	<i>Escherichia coli</i> microcosm	100	Kraupner et al. (2020)
	qPCR of ARGs from biofilm microcosm	100	Kraupner et al. (2020)
	Isogenic competition in planktonic system	17	Hjort et al. (2022)
Isogenic competition in biofilm system	23	Hjort et al. (2022)	

Adapted from Murray et al. (2021).

ARG = antibiotic resistance gene; LOEC = lowest observable effect concentration; MSC = minimal selective concentration; qPCR = quantitative polymerase chain reaction; OD = optical density; SELECT = Selection Endpoints in Communities of Bacteria.

potential (Karatzas et al., 2007). However, collateral sensitivity (whereby acquisition of resistance to one compound results in increased susceptibility to another compound) arising from triclosan (Curiao et al., 2016) and triclocarban (Carey & McNamara, 2016) exposure in *S. enterica* has also been documented. Beyond BAC and triclosan, chlorhexidine exposure has also been associated with increasing AMR (Kampf, 2019).

Zinc is used in numerous cosmetic products as an anti-oxidant, antiaging, antimicrobial, and anti-inflammatory agent (Abendrot & Kalinowska-Lis, 2018). In a single-species competition experiment, zinc increased the MSC of ciprofloxacin by fivefold, suggesting that zinc and ciprofloxacin behave antagonistically (Vos et al., 2020).

Though studies directly investigating selection for resistance by other PPCPs have not been performed, research indicates

they are warranted. For example, the anticonvulsant carbamazepine has been shown to increase ARGs in the *Folsomia candida* gut (Y.-F. Wang et al., 2020). Further, of 835 human-targeted non-antimicrobial pharmaceuticals, 24% inhibited growth of at least one bacterial species in vitro (Maier et al., 2018). Any reduction in growth could indicate a potential selective pressure (Greenfield et al., 2018; Gullberg et al., 2011, 2014; Murray et al., 2020). In addition, the insect repellents picaridin and *N,N*-diethyl-meta-toluamide have shown antimicrobial properties against bacteria, yeast, and fungal species (Kalayci et al., 2014). 2-Ethyl-hexyl-4-trimethoxycinnamate, an ultraviolet filter in sunscreens, caused reduced nitrification in a river sediment community (Xu et al., 2020), again suggestive of selective pressure. Parabens are used as preservatives in PCs, and resistance in bacteria is often mediated through similar mechanisms to antibiotic resistance (Bolujoko et al., 2021). To date, a single study has found little evidence to support co-selection of AMR by parabens when testing *Enterobacter geroviae* (Davin-Regli et al., 2006). Finally, linalool is an aromatic plant metabolite found in 60%–90% of cosmetic products and is used in detergents (Aprotosoai et al., 2014). A study exposing *S. enterica* serovar Senftenberg to linalool determined that resistance to five antibiotics increased and amikacin resistance decreased postexposure in comparison to non-exposed strains (Kalily et al., 2017).

## LABORATORY-BASED STUDIES INVESTIGATING HORIZONTAL GENE TRANSFER

Pharmaceuticals and personal care products can increase the mobility of ARGs by enhancing horizontal gene transfer (HGT). Elevated HGT rates increase the absolute abundance and potential microbial host range of ARGs. Through the ability to transfer to diverse hosts (Klümper et al., 2015), mobile traits encoded on plasmids increase their potential to persist and be selected and transported to novel environments (Hülter et al., 2017; Séveno et al., 2002). Further, HGT can result in ARGs transferring to pathogens. The three main HGT mechanisms, conjugation, transformation, and transduction (Gogarten et al., 2002; Zhaxybayeva & Doolittle, 2011) need to be considered to evaluate the effects of PPCPs.

Conjugation, the direct exchange of DNA between bacteria, is thought to be the most efficient HGT mechanism (Guglielmini et al., 2011; Halary et al., 2010). Effects of PPCPs on conjugation have been widely studied, evidencing that environmentally relevant concentrations of antibiotics regularly increase plasmid transfer rates within bacterial communities (Jutkina et al., 2016, 2018; Shun-Mei et al., 2018). In addition, this has been described for a number of non-antibiotic pharmaceuticals like carbamazepine, ibuprofen, naproxen, diclofenac, gemfibrozil, and propranolol (Y. Wang et al., 2018, 2021). The mechanism responsible for PPCPs elevating plasmid transfer rates is their ability to trigger the bacterial SOS stress response, increasing reactive oxygen species and cell membrane permeability (Y. Wang et al., 2021). Triggering the SOS response can induce

conjugation of AMR-encoding transposons from bacterial chromosomes (Seier-Petersen et al., 2014). Non-antibiotic pharmaceuticals have also been shown to trigger the bacterial stress response (Lagadinou et al., 2020), suggesting potential effects on transfer rates of AMR-encoding plasmids. Evidence also exists of metal cations (regularly used in PPCPs) altering plasmid transfer rates in soil communities in short-term (Klümper et al., 2017) and long-term (Song et al., 2020) exposures. Particularly strong effects were proven for metal nanoparticles of copper (Zhang et al., 2019) and silver (Lu, Wang, Jin, et al., 2020), which are used in antibacterial coatings in plasters, for example.

Transformation refers to bacterial uptake of free extracellular environmental DNA (eDNA). A small proportion of bacteria can absorb and integrate eDNA (i.e., competent cells). Competence occurs constitutionally or is induced by environmental factors (Hanahan, 1983; Nielsen & van Elsas, 2001). Pharmaceuticals and personal care products can induce bacterial competence or increase availability of free eDNA, promoting spread of AMR by transformation (Winter et al., 2021), as evidenced at environmentally relevant concentrations of antibiotics (Charpentier et al., 2012; Prudhomme et al., 2006), non-antibiotic pharmaceuticals (Y. Wang et al., 2020), and triclosan (Lu, Wang, Zhang, et al., 2020).

Finally, transduction, the indirect transfer of DNA by bacteriophages, relies on mistakes in viral packaging or prophage excision, during which genes from the current host are integrated into phage DNA (Watson et al., 2018). During infection, phage DNA is integrated into the host chromosome, including mispackaged former host's genes. Pharmaceuticals and personal care products affecting transduction through inducing prophages at environmentally relevant concentrations include antibiotics (Allen et al., 2011; Maiques et al., 2006) and nonantibiotic pharmaceuticals (Sutcliffe et al., 2021). These compounds are known to be able to cause oxidative stress inside the prophage hosting bacteria (Y. Wang et al., 2021), a common trigger for up-regulation of prophage excision from the chromosome (Liu et al., 2015). This leads to higher phage abundance and hence a higher transduction likelihood.

While these laboratory studies have demonstrated that PPCPs at environmental concentrations can influence HGT, their relative environmental contribution needs further investigation.

## FIELD-BASED STUDIES SHOWING EVIDENCE FOR EFFECTS OF PPCPS ON AMR

### Wastewater

Sewage treatment is necessary for sanitation (Hunt, 2006). Large-scale convergence of wastewater creates niches distinct from those in nature, resulting in significant ecological impacts at confluence points of wastewater and natural waters. Wastewater is a complex physiochemical and biological matrix (Newton et al., 2015) posing significant potential for selection of AMR by PPCPs. Healthcare-associated wastewater from hospitals or care homes contains elevated levels of PPCPs and

AMR because antibiotic/disinfectant use and carriage of AMR are more frequent in these populations (Hocquet et al., 2016). Hospital wastewater has significantly higher antibiotic residues than domestic wastewater (Aydin et al., 2019; Carraro et al., 2018; Paulus et al., 2019; Perry et al., 2021), with some concentrations far exceeding MSCs (Yao et al., 2021). For example, measured ciprofloxacin concentrations of 9900  $\mu\text{g/L}$  (Perry et al., 2021) are much higher than reported MSCs (5–10.77  $\mu\text{g/L}$ ; Bengtsson-Palme & Larsson, 2016; Kraupner et al., 2018; Stanton et al., 2020). However, concentrations vary across antibiotics, hospitals, and seasons. In the Pharmaceuticals in the Environment database (UmweltBundesamt, 2021), the median ciprofloxacin concentration from hospital wastewater (7.5  $\mu\text{g/L}$ ) was lower than that seen by Perry et al. (2021) yet remained within the MSC range.

Effluents from industry and pharmaceutical production are known to contain highly concentrated mixtures of PPCPs, far in excess of discharges from healthcare or domestic wastewater (Bengtsson-Palme & Larsson, 2016; Larsson, 2014). Domestic wastewater contains not only large volumes of unmetabolized antibiotics from widespread use and excretion from large populations but also incorrectly disposed of and unused PPCPs. Antibiotic concentrations of domestic wastewater are generally lower than those in healthcare wastewater in direct point-prevalence surveys. However, several studies normalizing total antibiotic loads in wastewater-treatment plant (WWTP) influent have shown that households can contribute more than point sources such as healthcare (Aydin et al., 2019; Santos et al., 2013; Verlicchi et al., 2012). While higher total loads do not necessarily result in antibiotic concentrations reaching MSCs after dilution, they may represent the accumulation of antibiotics in sewer sediments via sorption to biofilms (Jamheimer et al., 2004). This is expected to attenuate temporal flux of antibiotics, maintain supply to WWTPs, and potentially result in sewer hotspots with locally high antibiotic concentrations reaching MSCs.

These findings highlight the importance of domestic effluents as sources of PPCPs entering WWTPs. In addition, parabens are often used as preservatives in PCs, and paraben-resistant bacteria have been isolated from sewage-treatment plants in India (Selvaraj et al., 2013). However, based on the limited research conducted to date, parabens have not yet been definitively linked to co-selection of AMR (Davin-Regli et al., 2006).

Studies have found that HGT of AMR occurs in WWTPs, with antibiotics, polycyclic aromatic hydrocarbons, and WWTP processes promoting stress responses and phage proliferation (Woegerbauer et al., 2020). Bacteriophages carrying ARGs have been isolated from urban wastewater, which, when cloned into susceptible *E. coli*, rendered them resistant (Colomer-Lluch et al., 2014). Conjugative plasmids have also been demonstrated to facilitate persistence of ARGs (Che et al., 2019). Finally, Hutinel et al. (2021) found that although PPCPs (including antibiotics, biocides, and non-antibiotic pharmaceuticals) in municipal wastewater were unable to promote HGT, PPCPs from hospital wastewater increased the proportion of *E. coli* recipients of HGT (Hutinel et al., 2021).

Modern sanitation infrastructure is a closed system, which reduces human exposure to PPCPs and AMR. However, many

low- and middle-income countries lack WWTP infrastructure; thus, populations may be exposed to untreated wastewater from open drainage trenches or contamination of tap water (Tong et al., 2020). High-income countries with modern sewage systems minimize these risks but are reliant on effective treatment of waste. Failure to adequately reduce PPCP loads puts receiving environments at risk.

## Natural water environments

Natural water environments encompass marine and freshwater environments (including rivers, streams, lakes, coastal water bodies, and estuaries). Often, aquatic environments are exposed to and act as receivers of anthropogenic pollution, including treated and untreated domestic, hospital, and industrial wastewater; agricultural and other land-use runoff (e.g., landfill leachate, urban road runoff, and septic tank leakage); and aquaculture waters. This exposure facilitates the release of PPCPs into water bodies, allowing AMR to proliferate (Amos et al., 2015; Cabello et al., 2016; Williams et al., 2016). The development and spread of AMR in the environment is a result of the exposure of microbial communities to multiple stressors (e.g., mixed selective agents; Berendonk et al., 2015; McArthur & Tuckfield, 2000) and changing environmental conditions (e.g., nutrient concentrations and pH; Khan et al., 2017).

Measured environmental concentrations of PPCPs throughout natural water bodies vary substantially, depending on pollution inputs, sample type, and season. A common entry point of PPCPs into water bodies is from WWTP effluent. Pharmaceuticals are often not fully metabolized and, like some PCs, may not be eradicated during wastewater treatment. Pharmaceuticals and personal care products and their degradation products are found in complex mixtures in WWTPs (Backhaus & Faust, 2012; Brandt et al., 2015; Marx et al., 2015). For example, 56 unique pharmaceuticals were investigated in the effluent of 50 WWTPs, with hydrochlorothiazide detected in every sample; metoprolol, atenolol, and carbamazepine detected in 90% of samples; and antibiotics on average detected 56% of the time (Kostich et al., 2014). In a study examining sites up- and downstream of WWTP outflows, Amos et al. (2018) found higher levels of Class 1 integrons downstream and showed that QACs co-select for the mobilization of Class 1 integrons and *bla*CTX-M from environmental isolates. Similarly, Middleton and Salierno (2013) showed that triclosan-resistant isolates from surface water near WWTP outfalls were significantly more resistant to chloramphenicol and nitrofurantoin.

Untreated sewage can be discharged from combined sewage overflows (CSOs), contaminating the receiving environment. The impact of CSOs on AMR selection is understudied but has recently become a topic of public (BBC News, 2021), policy (Department for Environment, Food & Rural Affairs, 2021; Singer et al., 2021), and scientific (Eramo et al., 2017; Honda et al., 2020) interest. Socioeconomic factors can amplify wastewater contamination of water bodies. For example, some low- and middle-income countries lack wastewater-treatment and sanitation processes and directly dispose of fecal waste onto land or into water bodies (Segura et al., 2015). This can occur in

high-income countries, although concentrations are likely lower because of more effective wastewater treatment, improved antimicrobial stewardship, and policies that reduce pollution (e.g., European Union Water Framework Directive; Bougnom & Piddock, 2017; Nadimpalli et al., 2018; Vikesland et al., 2019). Data from rivers across 104 countries found that the highest concentrations of active pharmaceutical ingredients (APIs) in rivers (e.g., caffeine, metformin, paracetamol, sulfamethoxazole) were detected in lower-middle-income countries (categorized by using gross national income index; Wilkinson et al., 2022). Regions with less regulated access to medicines had greater variability and range of API concentrations (Wilkinson et al., 2022).

Release of PPCPs into water bodies from drug manufacturing effluent is also of concern. Often, antibiotic concentrations in pharmaceutical effluents far exceed MSCs (e.g., ciprofloxacin MECs 28 000–31 000  $\mu\text{g/L}$  [Larsson et al., 2007] exceeding the MSC of 10.77  $\mu\text{g/L}$  [Stanton et al., 2020]), posing a high risk for selection. This is also likely exacerbated by socioeconomic factors (e.g., in low- and middle-income countries; Segura et al., 2015). However, instances of concentrations reaching MSCs have been reported even after wastewater treatment in high-income countries (Babić et al., 2006; Phillips et al., 2010).

Another route by which PPCPs enter water bodies is through agricultural runoff. Pharmaceuticals are used in livestock rearing, as prophylactics, therapeutics, or growth promoters (Landers et al., 2012). This results in the transfer of PPCPs and AMR through livestock defecation and addition of fecal waste to farmland, inevitably ending up in water bodies (Lee et al., 2019). Pharmaceuticals and personal care products are also used in aquaculture and are administered in feed or directly released into water. Of the antibiotics ingested by fish, approximately 80% enter water and sediment via excretion (Cabello et al., 2013), resulting in fish farms being one of the most contaminated types of water body (Guruge et al., 2019).

There is a lack of data showing the effects of PPCP concentrations on selection for AMR in natural water bodies (Ebele et al., 2017; Fu et al., 2019; Luo et al., 2014). In the absence of realistic experiments, many studies infer risk of selection by calculating metrics such as risk quotients (as described above *Selection*). For example, risk quotients derived from MECs for 98 PPCPs in water environments in India showed that 81% and 38% of antibiotics detected in surface and groundwater, respectively, were at concentrations high enough to pose a risk of AMR selection (Sengar & Vijayanandan, 2022). That study is at the extreme end of the scale, and concentrations of singular PPCPs in natural water bodies are often not high enough to select for resistance alone. However, it is likely that the net effect of a mixture of antimicrobial compounds will exert a greater effect than each compound would exert individually (e.g., through additive or synergistic effects; Marx et al., 2015; Mitosch & Bollenbach, 2014).

## Soil environments

Soil represents one of the evolutionary origins of AMR (Cytryn, 2013; Forsberg et al., 2012; Nesme & Simonet, 2015), and soil-associated ARGs have been suggested as the primary

reservoir for clinical ARGs (Kim & Cha, 2021). Therefore, the contribution of PPCPs to the mobilization, maintenance, and dissemination of AMR in soil needs elucidation.

Manure, municipal waste, and treated wastewater irrigation are regularly input into soil environments during agricultural processes and have been identified as critical sources of AMR in soil (Cytryn, 2013). Biosolids and manure are valued resources of nutrients for crop growth and are commonly used as agricultural fertilizers (Case & Jensen, 2019; Subirats et al., 2021). Reuse of treated wastewater for agricultural irrigation is increasing in arid and semiarid regions of the world as a result of dwindling freshwater resources, expanding agricultural sectors, and the influence of climate change (Ungureanu et al., 2020). Such resources contain PPCPs, which may enter agricultural soils and elevate AMR levels. The bioavailability of PPCPs in the soil is dependent on their sorption and soil parameters (e.g., pH; Wegst-Uhrich et al., 2014). Soil antibiotic concentrations are strongly linked to land-use patterns, with agricultural land being the main source of antibiotics entering the soil (Zhao et al., 2020).

Antibiotic concentrations in soils amended with long-term manure application were significantly elevated in comparison to non-treated soils. Concentrations ranged from 81.50 to 178.99  $\mu\text{g/kg}$  and from 60.59 to 202.37  $\mu\text{g/kg}$  for tetracyclines and sulfonamides, respectively (Rahman et al., 2018). In addition, application of pig manure increased ARG levels for up to a year (Scott et al., 2018). A macrolide resistance gene, *ermB* persisted at high levels for a decade after manure application (Scott et al., 2018). Further, a 10 000-fold increase of four tetracycline ARGs was observed for manure amended soil in comparison to a control (Leclercq et al., 2016). Manure has been shown to increase the HGT of sulfadiazine resistance, with the application of manure and sulfadiazine increasing Class 1 integrons in soil (Heuer & Smalla, 2007).

Also, PPCPs can be found in soils amended with biosolids. Gottschall et al. (2012) monitored over 80 PPCPs in soil after application of dewatered biosolids. Dissipation of many PPCPs in biosolid-amended soils occurred within the first few months after application; however, PPCPs such as miconazole, triclocarban, and carbamazepine were still detectable over 1-year post-biosolid application at concentrations of 127, 22, and 30  $\mu\text{g/kg}$ , respectively (Gottschall et al., 2012).

Irrigation using reclaimed water has been shown to promote the maintenance of antibiotics in soils (Gao et al., 2015). Soils irrigated with treated wastewater generally have concentrations of antibiotics <10  $\mu\text{g/kg}$  (Biel-Maeso et al., 2018; Christou et al., 2017). In turn, those irrigated with untreated wastewater can contain concentrations ranging from not detectable to 2160  $\mu\text{g/kg}$ , with median values of 52.8 and 0.15  $\mu\text{g/kg}$  and not detectable for quinolone, sulfonamide, and macrolide antibiotics, respectively (Gao et al., 2015). Regarding the effect of PPCPs in reclaimed wastewater on AMR in soils, a study comparing agricultural soils irrigated with freshwater and treated wastewater found similar levels of AMR (Negreanu et al., 2012). However, long-term untreated wastewater irrigation had a significant impact on ARG levels in agricultural soils (Dalkmann et al., 2012).

The presence of antibiotics in the soil, even at sub-MIC concentrations, can select for antibiotic-resistant bacteria and enhance the transfer of ARGs and mobile genetic elements (Cycoń et al., 2019). Although no MSCs have been defined in situ in soil environments, Han et al. (2022) investigated the direct application of erythromycin fermentation residues (a by-product of the production of erythromycin) to soil, which is often used as organic fertilizer. Resulting concentrations of erythromycin in soil ranged from 0.83 to 76 µg/kg, and a significant increase in macrolide–lincosamide–streptogramin ARGs was observed gradually during the 3-year experiment (Han et al., 2022). Similarly, Brown et al. (2022) tested long-term (10 years) contamination of soil at high concentrations of three macrolides (10 mg/kg) and at concentrations similar to those detected in biosolids or manure (0.1 mg/kg). No effect was observed at 0.1 mg/kg, yet at 10 mg/kg, 21 clinically relevant ARGs and 20 mobile genetic elements increased (Brown et al., 2022). While this suggests that concentrations in manure and biosolids are not high enough to select for resistance, laboratory studies (described above) have shown that MSCs/LOECs vary significantly based on antibiotic type (Murray et al., 2021; Stanton et al., 2020), with macrolides having some of the highest MSC values (Murray et al., 2020; Stanton et al., 2020). Antibiotics with lower MSC values (such as ciprofloxacin [Kraupner et al., 2018; Murray et al., 2020; Stanton et al., 2020]) may be more potent, potentially resulting in increased levels of ARGs and mobile genetic elements, although MSCs for these antibiotics have yet to be derived in soils. These laboratory-derived MSCs are calculated from liquid experiments and are therefore represented in different units (i.e., micrograms per liter as opposed to micrograms per kilogram), making soil comparisons to these laboratory endpoints difficult. Further, the distinct properties of soil and changing behavior of PPCPs within soil (i.e., compound- and environment-dependent sorption and/or degradation; Chen & Akhtar, 2022) can also make laboratory endpoint comparisons complicated.

## IMPORTANCE TO HUMAN HEALTH

Increased levels of AMR driven by selection and HGT may result in increased exposure events when humans interact with the above environments, whether through recreational (e.g., swimming in designated bathing waters, swimming in natural waters that are not monitored for bathing water quality), occupational (e.g., WWTP worker), or essential (e.g., drinking water) activities.

A recent publication systematically compiled evidence on transmission of AMR from the environment to humans and found only 40 articles globally (Stanton et al., 2022). Papers investigated the risk of exposure to AMR in natural environments by calculating the burden of AMR in a particular volume of environmental matrix. Exposure risks were subsequently calculated based on the volume of matrices humans are exposed to (Stanton et al., 2022). For example, the number of third-generation cephalosporin-resistant *E. coli* in coastal water was determined, and ingestion estimates of different water

users were used to calculate exposure events during a bathing session (Leonard et al., 2015). Further, AMR exposure based on consumption of surface water-irrigated lettuce has been studied (O'Flaherty et al., 2019). Finally, estimated daily intake of ARGs via inhalation of airborne fine particles, ingestion of drinking water, and accidental ingestion of agricultural soil has been calculated (Xie et al., 2018).

Direct transmission of AMR from the environment to humans has also been investigated (Stanton et al., 2022). For example, surfers are four times more likely (following ingestion of coastal water) to be colonized by CTX-M-producing *E. coli* than non-surfers (Leonard et al., 2018). Further, 32% of reclaimed water irrigation workers were colonized by resistant *Staphylococci* compared to 4% of control office workers (Goldstein et al., 2017). While the exposure to AMR is occurring during an occupational activity, the source of the AMR is still environmental (reclaimed water).

Finally, Stanton et al. (2022) reported studies where AMR was transmitted from the environment following an accident and resulted in a human health outcome. For example, a near-drowning event in a river resulted in a carbapenemase-producing *Enterobacter asburiae* infection (Laurens et al., 2018).

Stanton et al. (2022) highlighted that transmission of AMR from the environment to humans is an underresearched topic area, with only 40 studies globally. However, within those 40 studies, water environments were studied most frequently ( $n = 40$  water environments, although, on occasion, the same study investigated more than one water exposure source). In contrast, only one study investigated the potential exposure to AMR from soil that could result in an adverse human health outcome (described above; Stanton et al., 2022).

Since the systematic map from Stanton et al. (2022), further work has been published investigating human health risks of exposure to environmental sources of AMR, with water environments continuing to be the focus of research on exposure risk. For example, Rodríguez-Molina et al. (2021) found that WWTP workers, residents who lived within 300 m of WWTPs, and residents who lived >300 m from a WWTP (as a control) carried 11%, 29%, and 7% extended-spectrum beta-lactamase Enterobacterales, respectively. This suggests that proximity and exposure to wastewater increase the risk of being colonized by antibiotic-resistant bacteria. In addition, Devi and Chattopadhyaya (2022) investigated colonization by extended-spectrum beta-lactamase *E. coli* of farmers who washed buffalo in earth ponds (37.5% rate of colonization) in comparison to age-matched household members who worked with the buffalo but did not wash them (20.7%), suggesting that transmission could occur from animal to human via a water source.

If AMR in natural environments increases as a result of selection, co-selection, or HGT by PPCPs, there will be an elevated risk to humans in contact with these environments, which could potentially result in a human health outcome. As demonstrated in the present review, selection, co-selection, and HGT can occur at environmentally relevant concentrations of PPCPs in water environments; and transmission of AMR can occur from water environments, resulting in a human health

outcome. However, there is a significant lack of research on selection, co-selection, and promotion of HGT in soil environments and on transmission of AMR from soil to humans.

## PRIORITY RESEARCH QUESTIONS

Below is a list of questions deemed a priority for tackling the development of AMR as a result of selection from PPCPs in the environment:

1. What are the MECs of PPCPs in various natural environments?
2. What are the MSCs of non-antibiotic PPCPs?
3. What are the in situ MSCs of PPCPs in the environment, and do these align with laboratory-derived MSCs?
4. What are the effects of PPCP mixtures on selection and HGT in the environment?
5. Does transmission from various underresearched natural environments result in a human health outcome?

## CONCLUSIONS

As evidenced throughout the present review, PPCPs are present in both wastewater and natural environments. There is a growing body of empirical evidence suggesting that environmental concentrations of antibiotics are often high enough to select for resistance and cause HGT, but until relatively recently there had been limited laboratory studies with mixed microbial community context. While there are limited data defining MSCs/LOECs for non-antibiotic PPCPs, a growing body of research suggests that these do affect both microbial growth and MICs. There is also evidence to suggest that non-antibiotic PPCPs affect HGT (e.g., by enhancing plasmid transfer rates). There is limited evidence of the effects of PPCP mixtures on selection and co-selection, even in laboratory studies, which could potentially exert a greater effect than the constituent compounds individually (Brown et al., 2022; Stanton, 2020; Vos et al., 2020).

Our understanding of the fate and effects of PPCPs in natural environments is incomplete (Ebele et al., 2017; Fu et al., 2019; Luo et al., 2014) and is exacerbated by the difficulty in performing in situ experiments because of an inability to control external factors such as exposure to a complex mix of selecting and co-selecting compounds, exposure to other pollutants, weather events, and other biotic and abiotic factors (Chow et al., 2015). Extensive research exists detailing relative concentrations of PPCPs and ARGs in natural environments, but knowledge gaps remain regarding selection, co-selection, and acquisition of AMR in these environments (Niegowska et al., 2021). Often, studies report the co-occurrence of PPCPs and AMR, using statistical associations, predictive modeling (Singer et al., 2019), or network analyses to infer selection. In the absence of in situ evidence of transmission and selection and any standardized guidelines on the environmental risk assessment for selection of AMR (Ågerstrand et al., 2015; Murray et al., 2021), many studies have taken to

calculating PNECs, MSCs and risk quotients, to give an AMR risk context to their findings.

If AMR does increase as a result of selection, co-selection, and HGT by PPCPs in the environment, as suggested by laboratory data, elevated PPCP concentrations in the environment will put people who interact with the environment at increased risk of both exposure to and transmission of AMR. There is a growing, yet still limited, body of evidence to suggest that transmission from the environment can occur, particularly from water environments. Addressing the priority research questions described in the present review will increase collective understanding of the effects of PPCPs on the selection of AMR in the environment. Complementary to this, reducing PPCP load, and therefore selection pressure, will reduce human exposure and transmission risk to AMR.

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