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The role of emerging organic contaminants in the development of antimicrobial resistance

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ABSTRACT

Antimicrobial resistance (AMR) threatens human and ecological health worldwide. Unless major changes occur across the human, animal and environmental sectors, the problem will continue to expand. An important component of AMR that deserves greater attention is the influence of emerging organic contaminants (EOCs) – ubiquitous compounds found, amongst others, in pharmaceuticals, personal care products, food, industrial and agricultural products, plastics and building materials. EOCs are widely used and can accumulate in the environment from varied sources, predominantly via waste streams. EOCs can interact with microbial communities potentially leading to the emergence and spread of AMR. Biocides and pharmaceuticals have been demonstrated to promote AMR development. Antimicrobial resistance is a multi-faceted problem that requires input from all sectors, with robust strategies and policies needed to make headway with solving the issues of this important threat.

1. Introduction

Development of antimicrobial resistance (AMR) is a "multifaceted problem" [1,2] threatening human and ecological health worldwide [3,4]. Common infections are becoming harder to treat, and there is a decreasing number of options remaining for treatment [5,6]. The incidence of AMR has risen mainly due to inappropriate use of antibiotics in human and veterinary settings [7], and from additional uses as growth promotors, metaphylactics and prophylactics in the animal husbandry and aquaculture industries [8,9].

It is well known that antibiotics contribute to the development of AMR [10–13], and as such is considered the main driver for the rise of AMR. Most research is based on the rise of AMR in clinical conditions [14], but there is also research that takes the environment into account as a reservoir for AMR spread [15,16]. A recent review by Bombaywala et al. [17] highlighted the current state of knowledge regarding the role of the environment in AMR spread.

From a global study of 76 countries, antibiotic consumption during the period 2000–2015 increased by 39% [18]. Despite global efforts to reduce the inappropriate use of antibiotics, it is expected to continue rising [19]. Global action plans have been developed to try and mitigate the rise in AMR [20,21]. Will these plans be successful in a reasonable time frame if they do not consider the connection between AMR and environmental factors [22]? Microbial communities in the environment are being exposed to anthropogenically produced or concentrated contaminants that stimulate the emergence of AMR [15,23]. One example is the relationship between trace element contamination and the development of AMR, which has been widely studied [24–26]. A recent review by Yu et al. [27] gave a wide overview of this problem in agricultural settings and highlighted that heavy metals can induce resistance to antimicrobial agents, but that organic minerals may not exhibit such a response. Many kinds of contaminants are

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unique to the last 100 years and have no history of being evaluated for effects on AMR [28,29].

Emerging organic contaminants (EOCs) are a large and diverse group of organic compounds that are not regulated nor frequently monitored in the environment, but have been detected in waterbodies and soils at concentrations that could impact ecosystem functioning [30,31]. These EOCs have also been linked with the induction and development of AMR [32–38]. Antibiotics and other biocides may induce AMR through their antimicrobial activity, but the effect is not limited to compounds with significant antimicrobial activity [39].

This review aims to update the current state of knowledge on the potential of EOCs to contribute to AMR in the environment and to increase awareness of the implications for antimicrobial stewardship. Given the extensive literature, including recent reviews [17] about the role of antibiotics in environmental AMR, this group of EOCs are not included in this paper.

1.1. Antimicrobial resistance

AMR is a natural phenomenon, in which bacteria, fungi, viruses and protozoa adapt to antimicrobial agents (antibiotics, antivirals, and antifungals) at previously lethal concentrations [5,40,41]. This makes treating infections tougher, and increases the risk of diseases spreading, development of severe illness and even death [5,41]. Many antimicrobial agents are produced by microorganisms, providing a selective benefit against competing bacteria [42,43]. Studies of antibiotic resistant bacteria (ARB) dominate the research, however, antifungal resistance is on the rise along with the consequences of resistance on both human health and the food industry [44]. Human behaviour governs the speed and extent at which AMR arises and develops, thus appropriate antimicrobial stewardship incorporating a "One Health" approach is required to help manage the problem [7,45].

1.2. Emerging organic contaminants

EOCs are a large group of synthetic or naturally occurring chemicals present in everyday products such as pharmaceuticals and personal care products (PPCPs), cleaning products, pesticides, building materials, plasticisers, flame retardants, veterinary, and industrial products [46]. They are found in all the same environments where bacteria, and more frequently resistant bacteria, are found too, such as livestock and poultry farms, sewage, sediments, hospital effluents and drinking water [47]. Some authors [48–50] also consider antibiotic resistance genes (ARGs) as EOCs, due to their persistence in the environment and ability to facilitate spread of resistance.

EOCs can be highly persistent [51,52], bioaccumulative [48] and frequently replenished in the environment. They are usually discharged into the environment via waste streams, potentially disrupting the natural regulation of ecosystems [30,31]. Degradation of persistent chemicals is challenging, so any contamination effects that follow on from discharge are hard to foresee [51]. Use and discharge of EOCs into the environment is largely unregulated and many are not routinely monitored in discharge or the wider environment, due to large contaminant numbers, lack of accurate analytical methods, and limited availability of toxicity data to establish safe levels [53–55]. The current number of chemicals used or released globally is around 350,000 [56] and over 150 million chemicals are registered with the chemical abstracts service (CAS) [57]. Since the 1950's over 140,000 chemicals and pesticides have been manufactured, with ~4% of those produced in high enough quantities to have widespread environmental dispersal and human exposure [29]. The actual number is unknown due to many factors, including chemical mixtures, which arise in storage or disposal, unregistered chemicals, and variability between national databases.

2. Sources of emerging contaminants to the environment

The predominant pathway of EOC entry to the environment is via wastewater discharge, but agricultural and aquacultural practises, industry and hospital inputs are also noteworthy (Fig. 1). Varying levels of EOCs have been detected in water and terrestrial environments, which may lead to unknown and unwanted downstream effects on freshwater and marine ecosystems [58]. Over 600 pharmaceutical substances have been detected across a range of environmental matrices with diclofenac, a nonsteroidal anti-inflammatory drug, the most frequently detected [59]. Around waste discharge points, higher concentrations of EOCs may increase the prevalence of ARGs and ARB and promote their spread [9,10,22,60–63].

2.1. Hospital waste

Hospital effluent is a source of many types of EOCs: therapeutic agents, biocide disinfectants, solvents and antibiotic residues, because it contains waste from research and diagnostic laboratories, patients and cleaning services [31,64,65]. Bacteria in hospital effluent have been shown to carry ARGs, such as the vancomycin (*vanA*) and methicillin (*mecA*) resistance genes [66–68]. The detection of ARB, such as extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli (E. coli),* multi-resistant pseudomonads and vancomycin-resistant enterococci (VRE) has been documented in hospital effluents [69–72]. Biocides such as antiseptics, disinfectants and preservatives used in hospitals transfer to wastewater [73–75]. Psychiatric drugs, non-steroidal anti-inflammatory drugs (NSAIDS), and antibiotics have also been detected in hospital effluent [76,77]. Integrase genes (such as *intI1*) have been detected and are associated with resistance determinants [78] and horizontal gene transfer, and ARGs themselves have been detected at 10^5 copies mL^{-1} in treated hospital effluent in Saudi Arabia [79]. Although hospital effluent is thought to have a higher pollutant load than that of municipal wastewater, once combined it represents ~1% of total municipal sewage [65,70,77].

Measures to treat hospital effluent vary widely between countries [80–82]. Hospital effluent is either co-treated with municipal wastewater, pre-treated in an on-site wastewater treatment plant (WWTP), and then transferred into a municipal WWTP, or directly discharged to surface water bodies without treatment. Onsite WWTPs could provide an extra treatment step, but the quality of the waste must be monitored to ensure reduction in contaminant levels.

2.2. Household waste

Household waste can contain a wide range of EOCs: PPCPs, disinfectants, detergents, cosmetics, pesticides, synthetic musk's, sweeteners and microplastics [83–87]. It is hard to characterise the contaminant content as it can differ widely, so is generally less well described compared to hospital effluent. Waste from individual households may be disposed of in landfills or toilets and goes to municipal WWTP or to on-site waste systems. A well-functioning on-site system has similar EOC removal efficiency compared to WWTPs [88]. However, infiltration of high contaminant-load waste to groundwater or surface water can occur and poses a risk to exposed ecosystems when on-site systems fail [89].

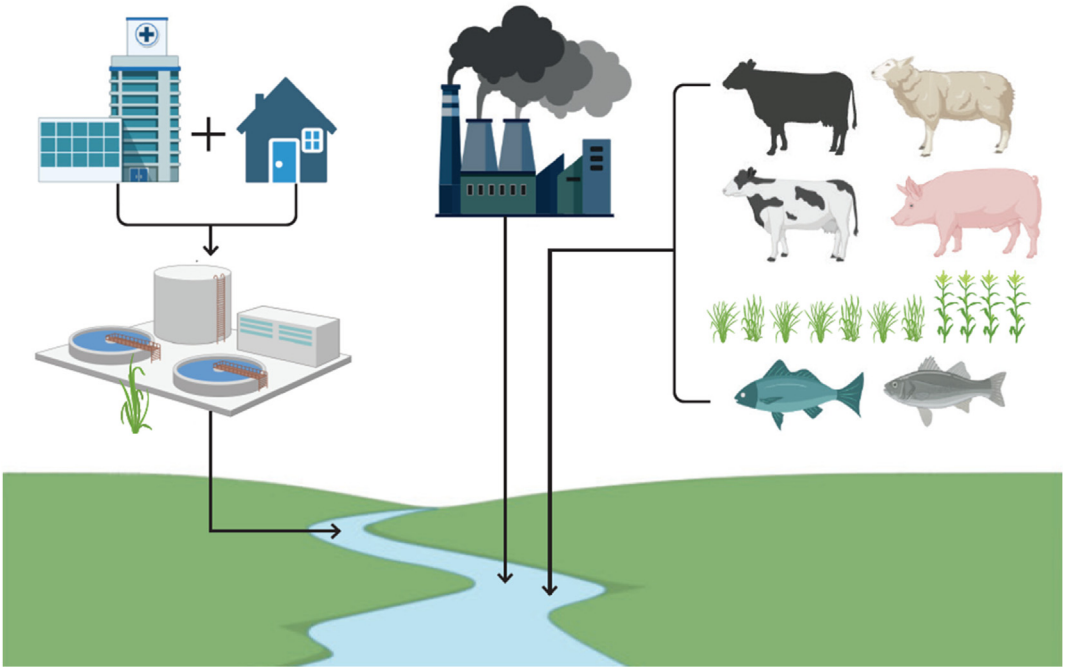

Fig. 1. Sources of EOC released into the environment. Hospital and municipal effluents both contain EOCs from different classes, which are predominantly treated at WWTPs. However, WWTPs may not remove all EOCs, which can then be discharged into the surrounding environment. Municipal effluents can also contain industrial wastes. Animal wastes can be re-applied to land, with EOCs potentially present that can affect soil microbial communities and leach into waterways impacting aquatic microorganisms. Aquaculture and horticultural activities may also be sources of EOCs. Created with BioRender.com.

2.3. Wastewater treatment plants

WWTP effluents are a main source of EOCs into the environment [9]. This is due to the persistence of some EOCs that are not effectively removed from municipal sewage inputs to WWTPs, which influences the load discharged into the environment [9,62,90]. A small proportion of EOCs may bind with high affinity to by-products of the WWTP process, such as sewage sludge [22],. Some EOCs can be recalcitrant and are found in the μg–mg L^{-1} levels within WWTPs [65] and at ng–μg L^{-1} levels in WWTP discharges [91]. Even at these low levels, some pose a risk to human and environmental health [92]. Advanced treatment technologies (e.g. ozonation, ultraviolet radiation) can effectively remove many EOCs, but are expensive and may not be accessible to smaller communities or developing countries [9].

2.4. Agriculture and aquaculture

Farm waste includes agrichemicals and effluent that is applied to land and contributes to water pollution via runoff [9,61]. Animal waste can contain EOCs [93–95]. Agricultural and aquaculture wastes have high nutrient content and are often applied to land as fertiliser. This practice may lead to contamination of the receiving environment with ARGs [95], disinfectants, endocrine disrupting chemicals and also inorganic contaminants including trace elements and halogens [96–98].

Land application of effluent as a source of EOCs has not been well characterised compared to WWTP discharge. Reuse of agricultural effluent spread to land as fertiliser, or as a simple disposal, has been demonstrated to increase the presence of ARGs [96,99–101] in soil with these genes able to persist for more than four months [102,103]. This may accelerate the distribution of resistance genes to other organisms present in the soil reservoir [94,102,103]. The levels of ARGs and ARBs present in the soil is influenced by land application methods (wastewater irrigation or manure application), what is applied, treatment methods for livestock waste and regional differences [61]. In both the agricultural sector and urban areas, there is substantial pesticide use and these types of EOCs can accumulate in the soil, leach to groundwater, and/or enter waterways via surface run-off affecting the exposed microbial communities [104]. Pesticides and other kinds of biocides are known to induce AMR [39,105,106].

Disinfectants, fungicides, detergents, and pharmaceuticals are used in aquaculture for feeding, prevention of biofouling and to limit infections. Many medicinal fungicides are commonly shared within the agricultural industry [107]. Evaluating the levels of antimicrobials used within the aquacultural industry is difficult, as the quantities used are unknown and reporting on substance use is substandard [108,109]. Industrial and household chemicals, ARGs, antibiotic residues and pharmaceuticals (from human and veterinary sources) have all been detected in aquaculture waters [109–111] and PPCPs in particular have been found in fish feed [112]. Contamination of aquaculture ponds can be a double-edged sword: local waterbodies can be used to fill the ponds, but these water sources have the potential to be contaminated. Thus, when additional EOCs are used in the aquaculture industry this leads to an accumulation of EOCs in the aquaculture ponds. Pond water can then be released back into the surrounding environment further compounding the problem [111].

2.5. Industrial waste

Industrial manufacturing may lead to the production of EOCs and with potentially high levels of chemical discharge, which can cause downstream effects on water quality, ecosystem health, and contribute to AMR [113]. For example, effluent samples from WWTPs from an industrial area of intensive antimicrobial agent production in India contained concentrations of EOCs at exceedingly high levels, that is in the mg L^{-1} range [114]. Perfluorochemicals, such as perfluorinated alkyl substances (PFAS),

have many industrial applications from biotechnology to food production [115] and are known to be bioaccumulative and persistent in the environment [116]. Benzotriazoles are complex agents used in the pharmaceutical production [117] and corrosion inhibitors [87] and are resistant to degradation. Industrial-use EOCs are commonly found in environmental matrices [118,119]. Although this is a serious source of environmental contamination, industrial inputs of antimicrobial agents into our environments are the least studied [90].

Antimicrobial agents are used in the food processing industry for sanitation and decontamination, but also included as additives and preservatives to help with extending shelf-life [120]. Tolerance to these preservatives and cross-resistance altering antibiotic susceptibility has been demonstrated [121]. Food stabilisers, thickeners and emulsifiers such as carboxymethyl cellulose and polysorbate 80, which are also used in cosmetics, pharmaceutical formulations and herbicides [39,122,123], have been shown to alter antibiotic susceptibility in *E. coli* and *Salmonella enterica* (*S. enterica)* [39]. Notably polysorbate 80, which causes bacteria to be more resistant to the antibiotic ciprofloxacin, was found in a patent for the drug's formulation at over three times the inducing concentration.

2.6. Urban runoff

EOC presence in stormwater runoff is under-researched, with studies only looking into the topic in recent years [124–127]. In a study by Fairburn et al. [125] 123 contaminants, a combination of pesticides, PPCPs, and polycyclic aromatic hydrocarbons (PAH), were detected in urban stormwater. Stormwater contamination can arise from building materials (copper and zinc from corroded surfaces), surface drainage and road washout (polycyclic aromatic hydrocarbons from road sealants) [127]. Washout from roads can contain high numbers of contaminants: PAHs from road sealants, chemicals from commercial car washes, car paint [127], microplastics [128], flame retardants and plasticisers [129]. Building materials can contain biocides used to prevent growth of lichen, moss, and mould. During rain events, residues of these chemicals can be released via surface run-off into storm water and then on to receiving soils or waterways [130,131]. Thus, it can be challenging to pinpoint the source of contamination to minimise EOC inputs. Regardless of source, there is also evidence that ARGs co-occur with EOCs in urban water environments [126,132].

3. Environmental role in AMR

Anthropogenic inputs into the environment that provide selective pressure on bacteria, combined with favourable environmental conditions, may promote the development and spread of AMR. The role of natural environments (such as freshwater) as a reservoir for the emergence and spread of AMR is not well understood [113,133,134]. Most research on AMR in the environment has focused on measuring the presence and abundance of AMR genes and bacteria and/or antibiotics in various settings [13,135–137]. Due to the obvious challenges, limited research has been undertaken to explore the actual impact of these findings on human, animal and environmental health [16]. The environmental resistome contains both naturally occurring AMR and AMR from anthropogenic sources and may act as a reservoir for the development of new resistance determinants [132,138]. Bacteria in areas with high anthropogenic input have increased capacity to allow easy passage of resistance genes amongst bacterial populations, when compared to natural transfer of ARGs due to increased selective pressures from the presence of EOCs [139].

Wastewater effluent discharge containing diverse microbial communities mixed with the resident endemic microbiota, and sub-inhibitory concentrations of EOCs represent ideal conditions for exchange of AMR genes [133]. WWTPs are considered 'hot spots' of development of AMR, as the environment inside the treatment plant ticks all the 'right' boxes to promote AMR. In addition, waste discharges can result in gradients of EOCs in the receiving environment at concentrations higher or lower than the bacterial minimum inhibitory concentration (MIC) for these compounds [140]. Exposure at concentrations well below the MIC can promote selection for resistance and also may alter a wide range of cellular responses such as stress response and the expression of bacterial virulence genes [140–142]. Within the treatment plant sewage sludge can act as a reservoir for resistance genes and common EOCs (PPCPs, biocides). Long retention times in sludge allow for the potential enrichment and establishment of a resistant community [143]. Application of sewage sludge onto land has been controversially discussed, especially with regard to suitable land use after application.

Agricultural practices can lead to AMR presence in the environment through manure application to land and animal grazing [104]. Once in the soil environment, numerous factors play a role in the persistence and potential transport of AMR into sub-surface, groundwater and surface waterways [9,13,22,144]. Although there is evidence of an increase in resistance genes from application of manure to soils, the cumulative effect and ARG persistence in soils is still not fully understood. A recent paper studied the persistence of antibiotic classes macrolide, sulphonamide and tetracycline ARGs in soil mesocosms amended with manure spiked with antibiotics [145]. There was a variation in the rate of dissipation of the ARG classes measured, with half-lives ranging from 4.65 days (*tetM*) to 10.68 days (*sul2*). The fact that variation appears to occur depending on antibiotic class implies that various mechanisms of persistence are related to the gene's specific bacterial host. When compared with the limited previous studies on persistence of ARGs in the environment from municipal sludge or manure amendment to soil, the authors suggest that more research is needed to ascertain the impact of soil type, ambient temperature, moisture on both ARGs persistence, and the survival of the bacterial hosts in the environment.

Transmission of ARB to humans is theoretically possible wherever we are exposed to them, but so far, the actual impact of environmentally acquired infections is not yet fully known. Potential AMR transmission routes to humans include: occupational exposure [61], food consumption [8,146], household pets [147], rodents [148], insects [149,150], recreational exposure [151] and environmental exposure via contaminated groundwater or surface water [94,152]. An example of the effect of anthropogenic antimicrobial drugs on environmental bacteria has been observed. The resistance genes *bla*CTX-M, *qnrA* and *bla*NDM originated from environmental bacteria, but have become relevant in the clinical setting due to selection through the use and over-use of therapeutic antimicrobial drugs [153].

4. Confirmed EOCs promoting AMR

EOC classes involved in the promotion of AMR include biocidal products such as the antibacterial agents triclosan [34] and triclocarban [154], antifungal agents such as the azole family of fungicides [44], herbicides [36], surfactants [36], but also some pharmaceutical agents such as salicylates [155], fluoxetine [35], ibuprofen [156], and carbamazepine [157]. Many of these commonly used medicines and commercial formulations were not envisioned as antimicrobial agents and their sub-lethal effects on bacteria are not routinely considered in how the products are used [158]. Often the concentration that triggers some form of bacterial

resistance doesn't match with the concentrations of these EOCs found across different environmental matrices (Table 1).

4.1. Biocides

Biocide use is widespread across hospitals, food processing and manufacturing facilities as disinfectants, but also as preservatives in pharmaceuticals, cosmetics or household products [75]. Disinfectants used in farming have been shown to increase the mutation rate in selected bacterial strains (*S. enterica* spp.) increasing acquired resistance to antibiotics [159,160]. Biocides used at sub-lethal concentrations are linked with AMR development, as resistance mechanisms may be shared between EOCs and antibiotics, which allows for resistance gene co-selection [22].

Triclosan (TCS), a prominent biocidal agent added to consumer products, is widely studied for its ability to contribute to AMR. Triclosan resistance has been associated with cross-resistance to antibiotics. *E. coli* and *Pseudomonas aeruginosa (P. aeruginosa)* exposed to TCS demonstrated a 10-fold increase in resistance to chloramphenicol and tetracycline after a 24 h period [161]. In trials using laboratory anaerobic digesters spiked with TCS or triclocarban, TCS-attenuated digesters were able to modify the microbial community to tolerate higher levels of antibiotics, with high levels of MexB (efflux pump component) present, whereas triclocarban attenuation reduced the antibiotic MIC of the biomass [32,162].

Quaternary ammonium compounds (QACs) are used as disinfectants and detergents. A study by Gaze et al. [163] found that there was a higher incidence of class 1 integrons in an environment where bacteria have experienced prior exposure to QACs compared to little to no prior exposure.

Azole fungicides are used in human and veterinary health agents, antifouling coatings, crop protection and timber preservation. This widespread use has accelerated the increase in resistance, with resistance simultaneously evolving in both the clinical and environmental setting [44]. *Candida auris* is an emerging nosocomial multi-drug resistant fungus with the ability to survive high levels of azole-based antifungals and disinfection due to efflux pump overexpression, point mutations and the ability to form biofilms for increased survival [164].

Similar mechanisms of resistance arise in agricultural settings [165]. Pesticides and herbicides are widely used in agriculture and can contaminate the surrounding soils, freshwater, surface water and groundwater [166]. Exposure to pesticides at environmentally relevant concentrations was shown to alter bacterial responses to antibiotics [39,167]. Three commonly used herbicides increased antibiotic MICs six-fold in experiments with *E. coli* and *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium), inducing adaptive changes to enable survival at higher antibiotic concentrations [36]. Interestingly, herbicide active ingredients and formulations were found to increase the MIC of some antibiotics and decrease it for others, in a species-dependent manner. Both effects were able to significantly increase the rate of evolution to acquired resistance [158].

4.2. Pharmaceuticals

The global pharmaceutical market is large and consumption rates are high. Many pharmaceuticals have been detected in groundwater [59], stormwater [125], surface water [168], and wastewater [169]. Essential medicines listed by the World Health Organisation; ibuprofen, diclofenac, naproxen, gemfibrozil, iopromide and propranolol have demonstrated their ability to promote ARG transfer by conjugation [170] and via bacterial transformation [171] at both environmentally and clinically relevant concentrations. Fluoxetine, a heavily prescribed anti-depressant can induce resistance to amoxicillin, chloramphenicol and tetracycline in *E. coli*. It is also a highly persistent and bioaccumulative compound in the environment [35]. Carbamazepine, an anti-epileptic, at environmentally relevant concentrations promoted the transfer of plasmid mediated ARGs between bacterial genera [157].

5. Resistance mechanisms induced by EOCs that promote AMR

Resistance to antimicrobial agents can be intrinsic or acquired [188]. Acquired resistance arises through a change in genotype caused by mutation or acquisition of a gene by horizontal gene transfer [11]. Mobile genetic elements such as integrons, plasmids and transposons enable the easy spread of AMR amongst bacterial populations [13,189], such as the exchange of resistance genes from pathogenic organisms to non-pathogenic and vice versa [190]. Fig. 2 illustrates the main mechanisms of AMR.

Intrinsic resistance can be phenotypically constitutive or induced, with the latter called “adaptive” resistance. Intrinsic resistance is a property of the species. For example, the outer membrane in Gram-negative bacteria creates a constitutive

Table 1
Emerging contaminant concentrations in the environment and levels at which resistance has been determined.

EOC class	EOCs	Environmental Concentration (μg L^{-1})				Concentration for resistance (mg L^{-1})	Reference
		Drinking Water	Effluent	Groundwater	Surface water		
Azole Fungicides	Clotrimazole		0.002 −8.65		0.007 −0.034	0.5	[172–174]
Biocides	Benzalkonium chloride		0.014 −2.5	0.2	1.9	0.063–5	[163,175–177]
	Chlorhexidine					0.063	[175,176]
	Triclocarban		0.4		0.005–0.01	30	[59,154]
	Triclosan	0.017	0.6	0.002–0.005	0.004–6.8	0.02–3	[35,37,59,161,176,178,179]
Herbicides	2,4, D		0.083 −0.11	0.08	0.73–1.85	1830–1950	[36,179–181]
	Roundup (or other glyphosate-based products)	1	0.3	2.1	0.02	1240–7000	[36,179,182–186]
	Kamba				0.73–1.04	≤1950	[36,181]
Pharmaceuticals	Fluoxetine	0.002	0.11	0.018	0.02	5–100	[35,59]
	Carbamazepine	0.17	0.498 −6.3	0.015–0.035	0.001–1.1	0.05	[59,157,178,179,187]
	Ibuprofen	0.02	1.36–3.4	0.32	0.005–0.53	0.05	[59,171,178,187]
	Diclofenac	0.14	1.02–2.1	0.05–0.037	0.1–1.2	0.5	[59,179,187]

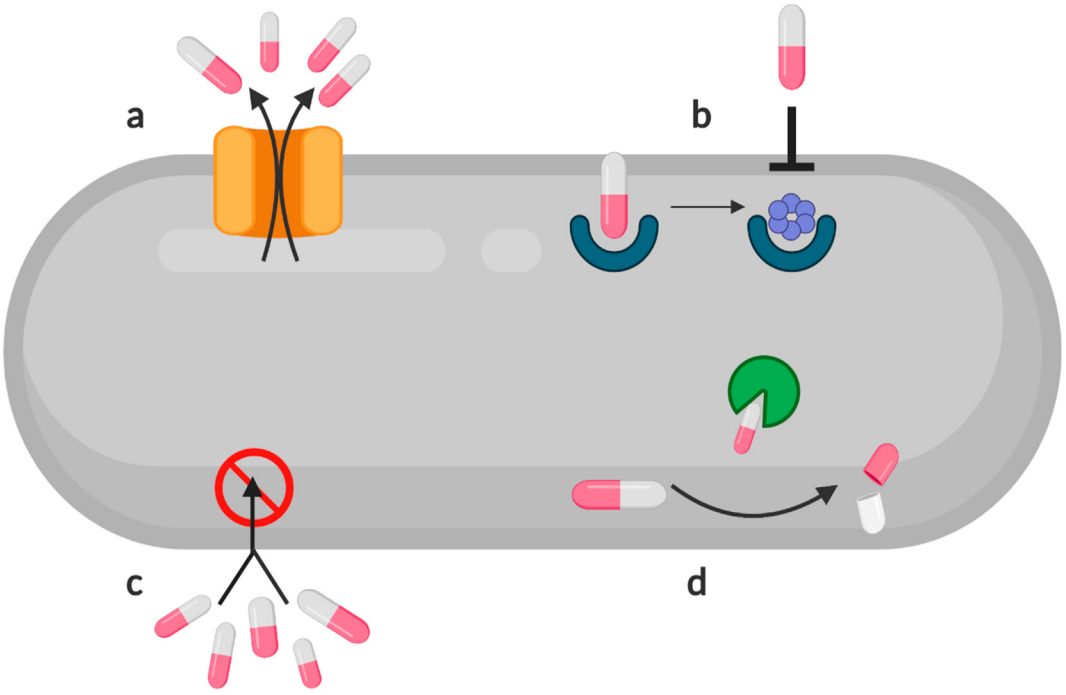

Fig. 2. Mechanisms of AMR. a) Efflux of antimicrobial agents, b) modification of antimicrobial agent target site, c) reduction in membrane permeability, and d) inactivation of antimicrobial agent [199,200]. Created with BioRender.com.

permeability barrier that can make Gram-negative species less susceptible than Gram-positive to some antibiotics. Regulated genes are present in all members of a species but may be expressed depending on the environment. Induction of genes for efflux pumps adapts bacteria to toxins in particular environments. Efflux pumps are used to remove toxic substances from the cytoplasm [191]. Genes for efflux pumps can also be acquired in some strains, such as when they are found on plasmids [192]. There are many efflux pump systems associated with clinically relevant bacteria such as *E. coli*, *Staphylococcus aureus* and *P. aeruginosa* [193–195]. As described in previous sections, EOCs have been shown to induce efflux pumps and pre-adapt bacteria to antibiotics.

Resistance to more than one drug can be achieved by co-resistance or cross-resistance [11]. Co-resistance happens when resistance genes are linked, as they can be when co-located on the same mobile genetic element and confer resistance to unrelated antibiotics [190,196,197]. Cross-resistance is where resistance is conferred by a single biological mechanism affecting a whole antibiotic class or different compound classes [190,197]. EOCs have been shown to contribute to both cross and co-resistance (Table 2).

Complicating antibiotic stewardship strategies is the finding that EOC exposures cause combinatorial effects with antibiotics. For example, exposure to herbicide formulations with dicamba along with salicylate pain relievers, each at concentrations too low to cause an effect, were additive for altering responses to antibiotics [36]. Antimicrobial stewardship is made more difficult because extremely low concentrations of antimicrobials are sufficient to influence the evolution of antibiotic resistance [198]. One of the more interesting effects of EOCs, seen with pesticides and triclocarban, is that they may decrease the MIC of an antibiotic. This indeed may be the more important effect in the environment, where antibiotic concentrations are generally lower than the MIC. By enhancing the effectiveness of the antibiotic, EOCs create selective pressure in environments that previously had too little antibiotic to influence competition between strains [158]. In contrast, where EOCs increase MIC they may be differentially important in medical settings because the antibiotic concentrations are maintained above MIC.

6. Future challenges

Over the last 50 years large numbers of new chemicals have been manufactured, some of them in high volume. However only a small percentage of those 'high volume' chemicals undergo rigorous testing for safety and toxicity [29], and none are not tested for effects on AMR development. Many EOCs are persistent and bioaccumulative [48,116,212], and a paucity of information about the fate and transport of EOCs in the receiving environment makes EOCs especially problematic [213]. These compounds are of most concern due to the prolonged selective pressure they may exert on microbes. The widespread distribution of EOCs makes it a challenge to reduce selective pressures on microbes.

In the future, chemical safety evaluations should routinely include the risk for AMR development prior to commercialisation. This foundational step would be a fundamental service to AMR stewardship. However, currently there are no standardised methodologies for establishing risk levels.

We suggest that future evaluations would be more possible if characteristics of EOCs could be identified that predict their likelihood to select for AMR. For example, chemically similar groups of EOCs or certain chemical features (such as specific functional groups) may predominate among those that favour AMR development. As chemicals with antimicrobial functionality [36,159,205,211] and non-antimicrobial functions [35,156,157] can stimulate AMR – what factors link these EOCs?

Furthermore, attention on persistent EOCs in pre-market assessment and policy making is lacking because the long-term effects of persistent chemicals are unknown. What adds to the challenge in regulating EOCs is that chemicals are likely to be found in complex mixtures and interact differently with one another, and

Table 2
Resistance mechanisms associated with bacteria after exposure to EOCs.

EOC class	Selected EOC	Bacteria used	Resistance mechanism	Associated antibiotics	Reference
Biocide	Benzalkonium chloride	*Campylobacter jejuni*, *Campylobacter coli*	Changes in outer membrane permeability Multiple efflux systems	Erythromycin and ciprofloxacin	[176]
		E. coli	Changes to outer membrane and increased efflux	Chloramphenicol	[201]
		S. enterica subsp.	AcrAB–TolC efflux *fabI* Potential changes to outer membrane	Ampicillin, chloramphenicol, ciprofloxacin and tetracycline	[38,160]
		S. enterica serovar Enteritidis	Upregulation of metabolism, protein synthesis, stress proteins. Downregulation of proteins for adaption and cell envelope formation	Amoxicillin, clavulanic acid, chloramphenicol, imipenem, polymyxin B, tetracycline, and trimethoprim	[175]
		S. enterica serovar Typhimurium	Changes in genes for metabolism, protein synthesis, efflux pumps, transcriptional regulators	β-lactams, polymyxin B, colistin	[202]
	Cetylpyridinium chloride	*Campylobacter jejuni*, *Campylobacter coli*	Changes in outer membrane permeability Multiple efflux systems	Erythromycin and ciprofloxacin	[176]
	Chlorhexidine	*Campylobacter jejuni*, *Campylobacter coli*	Changes in outer membrane permeability Multiple efflux systems	Erythromycin and ciprofloxacin	[176]
		S. enterica serovar Typhimurium	Changes in genes for metabolism, protein synthesis, efflux pumps, transcriptional regulators	β-lactams, poly-L-lysine, polymyxin B, colistin	[202]
	Triclosan	*Campylobacter jejuni*, *Campylobacter coli*	Changes in outer membrane permeability Multiple efflux systems	Erythromycin and ciprofloxacin	[176]
		E. coli	*acrAB* efflux, *marA*, *soxS*, *fabBAGI*, *ompR* *fabI*, *frdD*, *marR*, *acrR* and *soxR*	Chloramphenicol, trimethoprim, tetracycline, amoxicillin, amoxicillin/ clavulanic acid	[37,161,203–205]
		P. aeruginosa	MexCD - OprJ	Ciprofloxacin	[206]
		S. enterica serovar Typhimurium	AcrAB-TolC – *acrB soxS*, *fabBAGI*, *ompR* Changes in genes for metabolism, protein synthesis, efflux pumps, transcriptional regulators	Chloramphenicol, tetracycline, ampicillin	[202,203,207,208]
Disinfectants	QACs, tar acid-based disinfectant, oxidizing compounds, aldehyde-based disinfectant, halogenated tertiary amine compounds	*S. enterica* serovar Typhimurium	AcrAB-TolC efflux Reduced LPS O-antigen AcrEF-TolC efflux	Chloramphenicol, tetracycline, ampicillin	[159,209,210]
	Phenolic farm disinfectants	*E. coli* & *S. enterica* spp.	*AcrAB–TolC* efflux	Ampicillin, chloramphenicol, ciprofloxacin and tetracycline	[160]
Herbicides	Pyrethrin formulations, atrazine formulations, Dicamba formulations, glyphosate formulations	*E. coli* & *S. enterica* serovar Typhimurium	*soxS*, AcrAB, AcrAD-TolC efflux AcrAB-TolC efflux	Chloramphenicol, kanamycin, tetracycline	[36,167]
Pharmaceuticals	Fluoxetine	*E. coli*	AcrAB-TolC efflux, YadG/YadH transporter, Tsx channel, MdtEF-TolC pump ROS-mediated	Fluoroquinolones, aminoglycoside, β-lactams, tetracycline and chloramphenicol	[35]

react after release into the environment [214]. This makes it hard to determine levels of EOC use and to accurately predict environmental effects [51]. If persistent EOCs are also implicated in AMR development, then the potential accumulated environmental concentration needs to be considered rather than single measurements at particular concentrations that may not be representative over time.

The wider risk of AMR and the spread of ARB from the environment to humans is currently poorly characterised. There is no reliable way to quantify the volume of environmental ARGs and ARBs and their impacts on humans [139,215,216]. It is unknown what the threshold level of AMR, ARBs and ARGs in the environment are that could create a health risk for humans and animals. Undoubtedly, that risk will also vary when there are acute environmental events such as flooding or high winds. There is limited evidence [23,217] that transference between livestock to humans can occur, but we are far from being able to set limits on ARB or ARG presence that could be considered a risk. How ARG move in the environment to pathogenic or opportunistic bacteria which might lead to untreatable infections in humans is not well studied, but the long-term implications for public health are important.

Studies that have investigated the effects of EOCs [201,204,208,211] on the development of AMR are predominantly laboratory based, and translation to real-world environmental conditions is both difficult and limited. Concentrations of EOCs that trigger resistance are often above those found in the environment, however the lowest concentration that can trigger AMR selection in particular environments is unknown, but of high importance. In some cases, the EOC may increase susceptibility, and thus lower environmentally relevant concentrations of either it or an antibiotic are what create the evolutionary risk.

It is also unknown whether different environmental conditions (if any) might alter the concentrations at which EOCs can induce AMR development. Thus, more robust experimental strategies and

testing are needed to more fully address the environmental relevance of particular EOCs'. Research efforts should be focussed on environmental hot spot areas such as sewage effluent outfalls, sites of intensive agricultural activities, and hospital and veterinary wastes to facilitate identification of ARB and associated resistance mechanisms. This knowledge would assist the characterisation of EOCs to be considered priority in the modulation of the risks of AMR development.

7. Conclusion

There is no simple solution to the problem of AMR, including over simplified concepts of stewardship. Antibiotic usage is the primary driver of AMR and controlling use through stewardship is needed to mitigate the growing problem. However, even if new antibiotics were found with the ability to act on current ARB, there is a high likelihood that resistance will develop again and spread. This is because of the widespread and diverse resistance mechanisms already selected by evolutionary microbial competition, human use of previous generations of antibiotics, and the widespread contamination of the environment with EOCs. Overarching this are the choices societies make in the development and use of new drugs [45,218,219].

EOCs are increasingly being released into the environment via a variety of human activities. There is growing evidence that EOCs may have a role in the development and amplification of AMRs. Given the complexity of factors that promote AMR, a multi-faceted approach is necessary including stewardship of EOC compounds such as biocides, pesticides, and personal care products that also promote AMR.

Identifying the most important EOCs and the environments in which they are most prone to selecting AMR should be a priority. This type of information would assist in the development of better regulatory frameworks for the use of EOCs. Improving the treatment of wastes, a significant pathway of EOCs entering the environment is essential to complement these other requirements. The solution for this problem requires the implementation of effective policies and ongoing strategies as a collective rather than individual efforts, as all elements are linked. The current AMR global action plans lack emphasis on other EOCs as important contributors to AMR.

Declaration of competing interest

All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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