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Antimicrobial resistance: A new threat from disinfection byproducts and disinfection of drinking water?

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Abstract

Antimicrobial resistance is a global threat to public health. Recent research showed that residual disinfectants and disinfection byproducts (DBPs) might play an important role in promoting antimicrobial resistant bacteria and their genetic determinates, antimicrobial resistance genes (ARGs). This review summarizes the most recent understanding of the occurrence and mechanisms involved in the antimicrobial resistance induced by DBPs and its implications in widespread of antimicrobial resistance phenomena and human health in the drinking water realm. Disinfectants and DBPs, at both above−minimum inhibitory concentrations (MICs) and sub-MICs, could induce antimicrobial resistance via genetic mutations and/or horizontal transfer of ARGs. DBP-specific mutations were identified in new genes, as well as previously recognized ARGs, and they were all related to molecular mechanisms of antibacterial resistance. Studies of individual or mixture of diverse classes of disinfectants and DBPs at environmental concentrations (usually at sub-MIC levels) need to be conducted to confirm the reported findings.

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Keywords

Antibacterial resistance, Drinking water, Disinfection byproducts (DBPs), Mutations, Horizontal transfer.

Introduction

Antimicrobial resistance has become a critical public health issue worldwide [1−3]. Antimicrobial resistant bacteria (ARB) and their genetic determinates, antimicrobial resistance genes (ARGs), are regarded as emerging environmental contaminants with a widespread distribution in various environments, including water sources and drinking water systems [1,4]. Particularly, the rapid and widespread increase of new ARB and ARGs all over the world has been accelerated in recent years with the escalation of discharge of antibiotics and other pollutants into the environment [1−3,15]. As such, antimicrobial resistance has become an important theme in environmental and health science.

This review summarizes the most recent understanding of the occurrence and mechanisms involved in the antimicrobial resistance induced by DBPs and its implications in widespread of antimicrobial resistance phenomena and human health. Treatment processes of drinking water, particularly disinfection, contribute to the removal of ARB and ARGs [4,5]. However, recent research showed that disinfection byproducts (DBPs) [5−8] and drinking water distribution systems (DWDSs) [5,9] might play an important role in the enhancement of ARB and ARG. First, we summarized the occurrences, fate, and transport of ARB and ARGs through drinking water treatment and distribution systems. Then, we discussed the observed effects of DBPs in promotion and spreading of antibiotic resistance and current comprehension of the potential mechanisms involved. Although clinically relevant resistance by exposure to antibiotics above minimal inhibitory concentrations (MICs determined as the concentration of antibiotics that inhibits 90% of growth) has been the primary research focus [21], the occurrence and mechanisms for subinhibitory (10- to 100-fold below the MICs, referred to as sub-MICs) and more environmentally relevant concentrations to induce antibiotic resistance have only been demonstrated recently with much unknown [8,21]. Finally, we pointed out the knowledge gap and research needs in the area of the roles of antibiotic-like contaminants, such as drinking water DBPs, in the global threats of antibacterial resistance.

Presence of antimicrobial resistance bacteria and genes in drinking water

The identification and isolation of ARB in drinking water systems have been rather limited mainly because

of the inherent limitations in the conventional culture-dependent approaches, where ARB are identified and isolated by growing on culture media supplemented with antibiotics at MIC levels [1,10–12]. ARB that have been identified to be of great concern in drinking water systems include *Escherichia coli*, *Salmonella*, *Enterococcus faecalis*, *Pseudomonas* spp., and *Klebsiella pneumonia*. These ARB exhibited both monoresistance and multiresistance to a wide range of antibiotics [9,12–14].

ARGs are carried by ARB or exist as free DNA in drinking water, and the occurrences and diversity of ARGs in drinking water systems have been abundantly investigated by quantitative PCR worldwide [4,5,9,15–18]. The classification and functions of ARGs detected in drinking water systems were summarized in Table 2. These ARGs are responsible for activation of efflux pump, changes in permeability of cellular membranes, modification of antibiotic target sites, or/and deactivation of antibiotics [4,15,16,19]. And they can confer multiple resistances, or specific resistances to certain classes of antibiotics, such as aminoglycoside, beta-lactamase, macrolide, fluoroquinolone, sulfonamide, tetracycline, vancomycin, and others [4,12,19].

Although ARB and ARGs are widely present in drinking water sources, their origins and sources are yet to be elucidated [1,4,10,11,20]. They likely involve both anthropogenic activities that include the excessive use or misuse of antibiotics in clinic, agriculture and veterinary [19,21], and environmental stressors (such as nutrient deprivation, low/high temperature, low/high pH changes, and oxidative stress) that can enhance the effect of selective pressures and promote bacterial evolution toward antimicrobial resistance [1,9].

Fate of antimicrobial resistance bacteria and genes through drinking water treatment and in distribution systems

The fate and transport of ARB and ARGs through drinking water treatment processes and DWDSs remains largely unclear [2]. Disinfection processes, such as treatment with free chlorine, chloramine, hydrogen peroxide, and UV irradiation, in the drinking water treatment plants may contribute to the removal of ARB and ARGs [5,12,22–25]. However, drinking water distribution and plumbing systems have been suspected to play a role in the enhancement of ARB and ARG [4,9,26]. The relative abundances of both ARB and ARGs were found to be higher in the tap waters than those in the finished water at the treatment plants, presumably due to biofilm detachment [4,9]. The percentage of ARB of inlet finished drinking water, outlet tap water, and biofilms ranged from 0.26% to 9.85%, 1.08% to 16.29%, and 0.52% to 29.97%, respectively, in a chlorinated system and from 0.23% to 9.89%, 0.84% to 16.84%, and 0.35% to 17.77%, respectively, in a chloraminated system [9]. Similarly, the total enrichment of ARGs varied from 6.4- to 109.2-fold in tap water compared with finished water [4].

Recently, the role of residual disinfectants in the enrichment of ARB and ARGs in the DWDS has emerged as an intriguing research topic. Although the underlying mechanisms for the increased abundance of ARB and ARGs in DWDSs remains unclear, it is believed that biofilms in drinking water pipelines may facilitate the development and spread of antibiotic resistance via triggering stress responses [26,27] and promoting horizontal transfer of ARGs [9,26]. Although the well below-MIC levels of the residual disinfectants have been previously expected noneffective for inducing antibiotic resistance, recent evidence and enlightenment in sub-MIC resistance mechanisms pointed to the plausible causal relationship between disinfectants' residual and the increased ARB and ARGs in DWDSs [8,9,12,21]. The residual disinfectants at the sub-MIC level may lead to *de novo* induction of antimicrobial resistance via cross-resistance, coresistance, mutagenesis, and horizontal transfer of ARGs [1,12,28,29], which are further discussed in the following section.

DBPs lead to antimicrobial resistance

There has been emerging evidence that DBPs can lead to antimicrobial resistance (Table 1). Oxidative and mutagenic DBPs, at above-MIC levels, have been shown to increase antimicrobial resistance by stimulating chromosome mutations [6–8]. A number of DBPs, including dibromoacetic acid, dichloroacetonitrile, 3-chloro-4-(dichloromethyl)-5-hydroxy-2 [5H]-furanone, trichloroacetic acid, iodoacetic acid (IAA), bromate (BrO_3^-), and Chlorite (ClO_2^-), at above-MIC levels, have been proved to select and induce resistant mutations with hereditary stability [6–8]. In addition, there have been verification that above-MIC levels of DBPs and disinfectants decreased the horizontal transfer of ARGs in drinking water by repressing the conjugative transfer via inactivating both donor and receipt bacteria [29,30].

As the environmentally relevant concentrations of DBPs in DWDSs are relatively low and usually at sub-MIC levels (as in reference to regulation standards shown in Tables S1 and S2), whether these sub-MIC levels of DBPs can lead to induction of antimicrobial resistance has hardly been evaluated and is an open area for systematic and mechanistic investigation. Our recent studies have shown that sub-MIC levels of two DBPs, IAA and ClO_2^-, induced mutations that exhibited clinically relevant resistances to amoxicillin and ciprofloxacin, as well as multiresistances to other antibiotics (gentamycin, polymyxin B, tetracycline, and erythromycin) [8]. More importantly, the sub-MIC levels of these two DBPs were used to select strains with resistance higher than those evolved under above-MIC

Table 1

Summary of studies on disinfectant- and DBP-induced antimicrobial resistance.

DBPs and disinfections		Tested concentrations	Mechanisms	Antimicrobial resistance phenotypes	Methods	Ref.
DBPs	DBAA	Sub-MICs (200 and 400 mg/L); Above-MICs (600–1600 mg/L)	Induction of AR via mutagenesis	• DBAA, DCAN, $BrO3^-$, and MX induced specific and multiresistance to ten antibiotics (carbenicillin, chloramphenicol, clarithromycin, gentamicin, polymycin B, tetracycline, cefotaxime, norfloxacin, rifampin, and ciprofloxacin). • Potential and rank of the DBPs in enhancing ARB: MX > BrO_3^- > DCAN > DBAA.	• The resistant mutations were isolated and determined by using LB agar containing antibiotics. • Selected genes of MX-induced mutants were sequenced.	[6,7]
	DCAN	Above-MICs (20–240 mg/L)	Induction of AR via mutagenesis			
	$KBrO_3$	Above-MICs (334–4008 mg/L)	Induction of AR via mutagenesis			
	MX	Above-MIC (0.1–20 mg/L)	Induction of AR via mutagenesis. Genetic mutations were identified in *gyrA, gyrB, parC, parE, rpoB, rpoBNC, mexR, nfxB*, and *mexZ* genes.			
	TCAA	Above-MIC (64 mg/L); Sub-MIC (10 mg/L)	No induction of mutations.	Did not induce resistant mutations.	• The resistant mutations were isolated and determined using LB agar containing antibiotics. • The resistant mutations were analyzed by whole-genome sequencing.	[8]
	ClO_2^-	Above-MIC (400 mg/L)	Induction of AR via oxidative stress with mutations identified in genes related to (i) membrane structure and transport (*frdD, glpF exbB*); (ii) transcription and translation (*rpoS, firmE*), and (iii) unknown functions (*ylbE*).	• These two DBPs, at both above- and sub-MIC levels, selected strains that exhibited clinically relevant resistances to amoxicillin and ciprofloxacin with fourfold to eightfold increase in MICs. • Mutations exhibited multiresistances to other antibiotics with < fourfold increase in MICs. • The ciprofloxacin-resistant strains induced by sub-MICs DBPs showed significantly higher resistance than those induced by above-MICs DBPs.		
		Sub-MIC (10 mg/L)	Induction of AR via oxidative stress and SOS response, with mutations related to (i) transcription and translation (*gryA,* and *proS*), (ii) membrane transport (*marC* and *uhpT*), and (iii) intergenic spacer (IGS).			
	IAA	Above-MIC (350 mg/L)	Induction of AR via oxidative stress and SOS response with mutations related to (i) membrane structure and transport (*dsdX, and kup*); (ii) transcription and translation (*rpoS*), and (iii) unknown functions (*ylbE*).			
		Sub-MIC (10 mg/L)	Induction of AR via oxidative stress and SOS response, with mutations related to (i) transcription and translation (*gryA,* and *proS*), (ii) membrane transport (*uhpT, marR, secF*), and (iii) IGS.			
Disinfectants	Free chlorine	Above-MICs (5 and 10 mg/L) Sub-MICs (0.1–1 mg/L)	Depress conjugative transfer. Promote conjugative transfer of ARGs by generating intracellular ROS, increasing cell membrane permeability, inducing oxidative stress and SOS response, and altering expressions of conjugation-relevant genes.	• The above-MIC disinfectants decrease conjugative transfer of ARGs by inactivation of both donor and recipient bacteria. • The sub-MIC disinfectants promote conjugative transfer of ARGs	•Intragenera transconjugants were detected by LB plates with 20 mg/L Chl and 100 mg/L Km. • Intergenera transconjugants were isolated by LB agar plates with 20 mg/L Chl and 100 mg/L Amp.	[29]

(*continued on next page*)

Table 1 (*continued*)

DBPs and disinfections	Tested concentrations	Mechanisms	Antimicrobial resistance phenotypes	Methods	Ref.
Chloramine	Above-MICs (5 and 10 mg/L) Sub-MICs (0.1–1 mg/L)	Depress conjugative transfer Promote conjugative transfer by generating intracellular ROS, increasing cell membrane permeability, inducing oxidative stress and SOS response, and altering expressions of conjugation-relevant genes.			
H_2O_2	Above-MICs (6–60 mg/L) Sub-MICs (0.24–3 mg/L)	Depress conjugative transfer Promote conjugative transfer by generating intracellular ROS, increasing cell membrane permeability, inducing of oxidative stress and SOS response, and altering expressions of conjugation-relevant genes.			

ARB, antimicrobial resistant bacteria; ARGs, antimicrobial resistance genes; MICs, minimum inhibitory concentrations; ROS, reactive oxygen species; DBPs, disinfection byproducts; DBAA, dibromoacetic acid; DCAN, dichloroacetonitrile; LB, Luria-Bertani broth; MX, 3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]-furanone; TCAA, trichloroacetic acid; IAA, iodoacetic acid; BrO_3^-, bromate; ClO_2^-, chlorite; Amp, ampicillin; Chl, chloromycetin.

exposure concentrations. The whole-genome sequencing results further revealed the mechanisms for sub-MICs' induction of antibiotic resistance, which involve both recognized resistant genes and pathways, as well as new and unknown resistant genes and associated pathways [8]. Furthermore, sub-MIC levels of DBPs and disinfectants, such as free chlorine, chloramine, and hydrogen peroxide, at sub-MIC lethal levels, could accelerate the horizontal transfer of ARGs in drinking water by increasing cell membrane permeability, inducing SOS response and recommendation, and regulating the expression of conjugation-relevant genes [29,30].

To date, there have only been limited reports on the induction of antimicrobial resistance by a small number of DBPs. There are more than 700 identified DBPs in drinking water, and they occur as a mixture in drinking waters [31,32]. The mixture effects of DBPs on selection of antibiotic resistance have not yet been investigated. Based on the concentration additive model of mixture toxicity, it is likely that the mixture of various DBPs in drinking waters may have higher impact on those broadly conserved cellular functions and pathways, such as those involved in bacterial oxidative stress and SOS response systems, than individual chemicals [21,28,31,32]. Thus, it is expected that DBP mixtures may play a more significant role in selection of antibiotic resistance than single DBPs.

Mechanisms involved in the induction of antimicrobial resistance by DBPs in drinking water systems

The recognized mechanisms involved in the induction of antimicrobial resistance by DBPs in the drinking water systems are summarized in Figure 1 and Table 1. Acquisition and dissemination of ARB and ARGs mainly involve two principle mechanisms, namely genetic mutations in chromosomal genes and horizontal transfer of ARGs that are generally located on mobile genetic elements, such as plasmids, transposons, and integrons [1,21,33–35]. The antibiotic resistance induced by DBPs and disinfectants can be categorized by coresistance (different resistance determinants present on the same genetic element), cross-resistance (the same genetic determinant responsible for resistance to both antibiotics and DBPs), and coregulation [28,36,37]. The mechanisms involved are distinct depending on the exposure concentration at either sub-MIC or above-MIC levels, and they not only include those genes in commonly recognized antibiotic resistance pathways related to activation of efflux pump, changes in permeability of cellular membranes, modification of antibiotic target sites, and deactivation of antibiotics but also contain genes that have not been previously identified to be associated with antibiotic resistance, as shown in Figure 1 and Table 1.

Table 2

Summary of classification and functions of ARGs detected in drinking water systems.

Classification	Resistance mechanism	Name of ARGs	References
Aminoglycoside resistance	Production of aminoglycoside acetyltransferase for deactivation of aminoglycoside	*aac, aacC1, aacC2, aacC4, aacC, aadA5, aadA1, aadA2, aadA, aadD, aadA9, aadE, spcN, aphA3, aph6ia, aph, aphA1, str, strA, strB*	[4,19]
Beta-lactamase resistance	Expression of enzymes for degradation of beta-lactamase	*blaSHV*, *blaVEB*, *bla1*, *blaOKP*, *blaROB*, *cfxA*, *blaZ, blaTEM*, *penA*, *pbp2x*, *blaPER*, *cfiA*, *cphA*, *blaVIM*, *blaIMP*, *blaCMY*, *blaOCH*, *blaPAO*, *ampC*, *fox5*	[4,16,19,24]
	Preventing from inhibiting cell wall synthesis	*Pbp5*, *pbp*, *mecA*	
Macrolide, lincosamide, streptogramin B (MLSB) resistance	MLSB efflux pumps	*msrC*, *msrA*, *vgaA*, *vgaB*, *vgbB*, *msrA*, *oleC*, *carB, mdtA*, *mefA*	[4,19]
	Expression of macrolide resistance methyltransferase	*ermK*, *ermF*, *erm(36)*, *ermB*, *ermT*, *ermX*, *ermY*, *ermA*, *ermC*, *pikR1*, *pikR2*	
	Deactivation of macrolide, lincosamide, and streptogramin B	*ereA*, *vgb*, *mphB*, *mphA*, *mphC*, *lnuB*, *vatD*, *vatE*, *vatB*, *vatC*, *vatE*, *vatB*, *lnuA*	
Fluoroquinolone and chloramphenicol resistance	Change the target of fluoroquinolone	*gryA, gryB, catB3-2, cfr-2, catA1*	[4,19]
	Fluoroquinolone and chloramphenicol efflux pumps	*floR-2*, *yidY/mdtL*, *cmlA1*, *cmx(A)*, *mexE*, *mexF*, *emrB/qacA*, *pmrA*, *acrB*, *acrF*, *adeA*, *cmeA*, *mexA*, *mexD*, *oprJ*, *acrA*	
Sulfonamide	Change the target of sulfonamides, which is the enzyme dihydropteroate synthase in the folic acid pathway.	*sul*(I), *sul2*, *sulA/folP*, *sulA/folP*, *sulA/folP*	[4,19]
Tetracycline	Expression proteins that confer resistance to the protein synthesis inhibitor tetracycline	*tet(36)*, *tet(32)*, *tetO*, *tetQ*, *tetM*, *tetW*, *tetS*, *tetPB*, *tetT*	[4,19]
	Tetracycline efflux pump	*tetA*, *tetPA*, *tetD*, *tetR*, *tetC*, *tetG*, *tetK*, *tetH*, *tetB*, *tetL*, *tetV*, *tetJ*, *tet(38)*, *tetE*	
Vancomycin	Cellular protection	*vanA*, *vanB*, *vanHB*, *vanWB*, *vanXB*, *vanRB*, *vanSB*, *vanYB*, *vanC*, *vanTC*, *vanC1*, *vanRC4*, *vanSC*, *vanD*, *vanG*	[4,19]
	Reduce the ability of vancomycin to diffuse into the division septum of the cell		
Others	Efflux pumps	*marR, cmr, sdeB, mepA*, *emrD*, *mdetI1*, *yceE/mdtG*, *yceL/mdtH*, *rarD*, *qacA/qacB, ttgB, ceoA*, *mdtE/yhiU*, *acrR*, *mtrD*, *mtrE*, *oprD*, *ttgA*, *mtrC*, *tolC*, *qacH*, *qacEΔ1*, *qac*, *qacA*	[4,19]
	Deactivation of antibiotics	*catB8*, *dfrA1*, *dfrA12*, *folA*, *ereB*, *fosX*, *yyaR*, *fosB*, *bacA, fabK, sat4*	
	Transposase	*tnpA*, *IS613*, Tp614, *tnpA*	

ARGs, antimicrobial resistance genes.

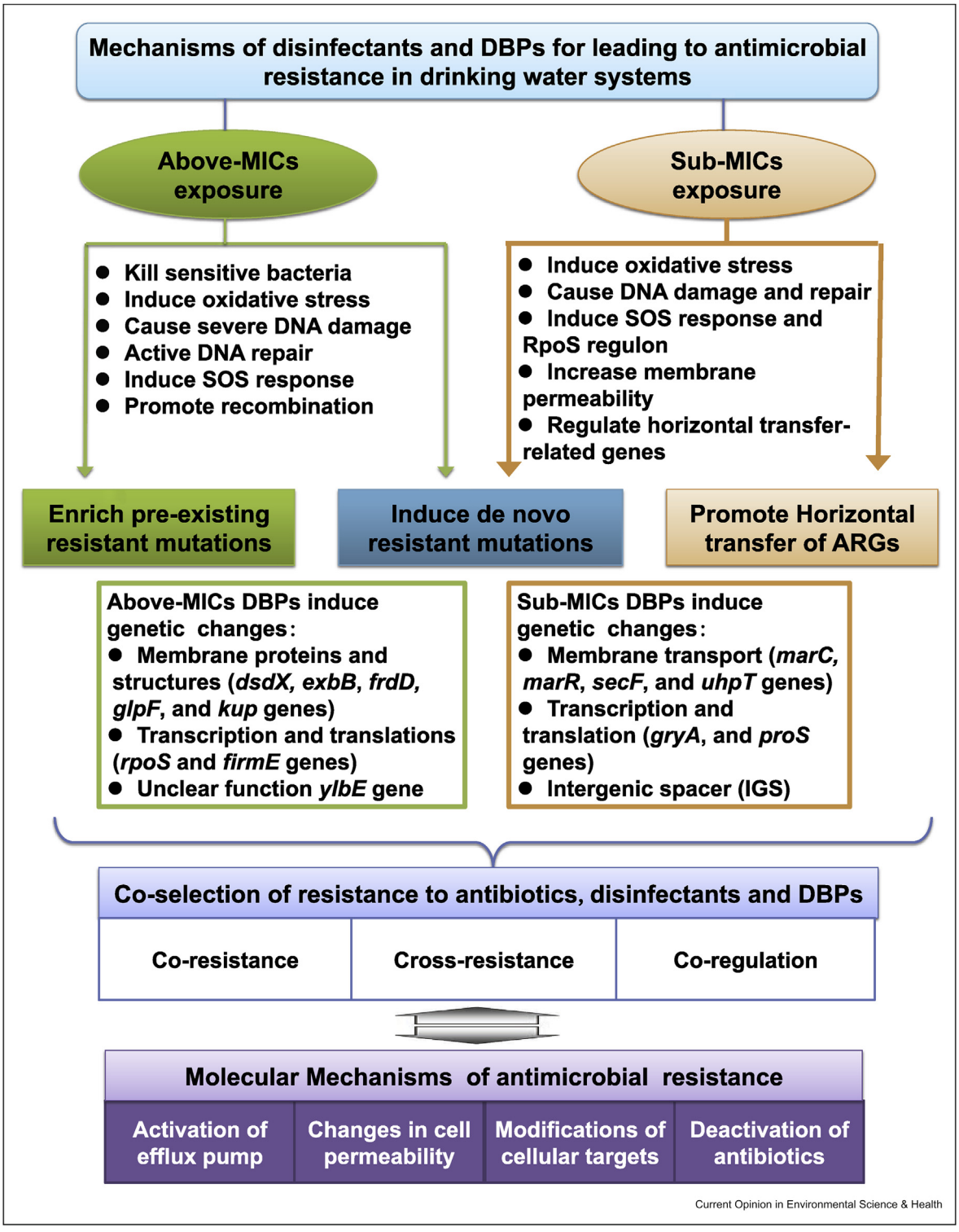
Antimicrobial resistance induced by DBPs at the above-MIC level

It is traditionally assumed that selection of resistant bacteria occurs only at concentrations above the MIC of the susceptible wild-type population and that concentrations below the MIC will not inhibit growth of the susceptible bacteria and therefore will not exert selective pressure [21,38]. The mechanisms for above-MIC levels of DBPs leading to antimicrobial resistance involve the following: (1) killing the sensitive bacteria and simultaneously enriching the pre-existing spontaneous mutations and (2) inducing *de novo* resistant mutations via inducing oxidative stress, causing sever DNA damage, activating the SOS response, inducing error-correcting repair systems, and homologous recombination [8,28,31,32]. Whole-genome sequencing of the resistant cells induced by DBPs at above-MIC levels identified mutations in genes previously shown to be involved in either antibiotic-specific or multidrug resistance pathways related to membrane proteins and structures, transcription and translations, or with unclear functions (Figure 1) [6–8]. However, mutations in genes that were not previously known to be involved in any antibiotic resistance were also identified, which may potentially play critical roles in antibiotic resistance, thus warranting further investigation [6–8].

Antimicrobial resistance induced by DBPs at the sub-MIC level

The role of widely present DBPs at relatively low concentrations (sub-MIC levels) in the selection and enrichment of antibiotic resistance is of great interest and importance, and the underlying mechanism needs to be systematically explored. Sub-MIC DBP exposure can increase intercellular reactive oxygen species, such as hydroxyl radicals, which can directly cause oxidative stress and DNA damage, induce SOS response, activate the DNA repair systems, and promote homologous

Figure 1



Possible mechanisms involved in antimicrobial resistance induced by DBPs in drinking water systems. DBPs, disinfection byproducts; MICs, minimum inhibitory concentrations; ARGs, antimicrobial resistance genes.

recombination, leading to accumulation of *de novo* resistant mutations with lower fitness cost comparing with those that occur at above-MIC DBP exposure (Figure 1) [6–8,31,32]. Prolonged exposure of bacteria to sub-MIC levels of DBPs likely generate a state of high mutation frequency and greater mutational space in different chromosomal loci for a small portion of the population and favors the accumulation of progressive

multiple small-step mutations for bacteria to form a wide range of mutant phenotypes [4,8,21]. In contrast, above-MIC DBP exposure induces and selects very specific mutations with higher resistance phenotypes that assist in cell survival [6–8,21].

Li et al. showed that ClO_2^- and IAA at sub-MIC levels induced mutations, rendering higher resistance than those selected under above-MIC exposure [8]. Whole-genome sequencing analysis of the induced resistant strains showed distinct mutations between the resistant strains induced with either above-MIC or sub-MIC DBP exposures [8]. The mutations were localized to only a small set of genes (7–8) belonging to three major functional groups, including transcription and translation, membrane transport, and intergenic spacer. Some of these genes were already known to be involved in multiple drug and drug-specific resistance, and some of them were identified for the first time to possibly play a role in antimicrobial resistance [8].

Sub-MIC levels of DBPs can also promote horizontal transfer of ARGs among bacteria, which is another important driving force for the dissemination of ARGs in drinking water systems [26,29,30]. Zhang et al. [29] investigated the effects of three disinfectants (free chlorine, chloramine, and hydrogen peroxide) on promoting conjugative transfer of ARGs within and across genera. The results indicated that the sub-lethal level of these disinfectants could enhance the conjugative transfer efficiencies. The underlying mechanisms involve generating intracellular reactive oxygen species, inducing SOS response, increasing cell membrane permeability, and altering regulation of horizontal transfer–relevant genes that comprise global regulator genes, mating pair formation (Mpf) system genes, plasmid transfer, and replication (Dtr) system genes (Figure 1) [29]. As many DBPs at sub-MIC levels can also induce intercellular hydrogen peroxide via oxidative stress, we speculate that many sub-MIC levels of DBPs can also accelerate horizontal transfer of ARGs. The effects of the large number and diversity of DBPs on horizontal transfer of ARGs, especially at relatively low concentrations in drinking water systems, however, have yet to be elucidated.

Impact of DBPs on disinfected drinking water on human gut microbiome and resistome

Drinking water may be one of the most important factors that impact the human microbiome and resistome, which have been hardly explored so far [39–42]. In a recent study, mouse gut microbiota was significantly impacted by the ingestion of different types of drinking water, including autoclaved tap water (as control), water collected directly from a drinking water treatment plant, tap water, and commercial bottled mineral water [43]. Two clinically important ARB, including *Acinetobacter* and *Staphylococcus* genera, increased in feces of mice that drank tap water and in mucosa-adhered samples of animals which consumed disinfected water from a drinking water treatment plant and tap water groups. However, the mechanism for how drinking water impacts gut microbiota is still largely unknown. In addition, there is no study on the ARGs in human gut microbiota on ingestion of different types of drinking water with varying DBPs, which should be addressed by further studies, because the interaction of drinking water and DBPs with gut microbiota could be a potential route for induction of ARB and ARGs.

Conclusions and future perspectives

The objective of this review was to provide phenomenal observations and mechanistic insights of antimicrobial resistance induced by disinfected drinking water and the DBPs generated in the disinfection process. Even though a large number of DBPs have been recognized to be ubiquitous in drinking water systems, unknown DBPs are continuously being identified, particularly those associated with disinfection technologies, such as UV and ozone [31,32]. The toxicity of most DBPs remains poorly understood, with one of the biggest knowledge gaps being their effects on antimicrobial resistance in drinking water systems and consequent implications in public health. Based on both molecular toxicity assessments and quantitative structure–activity relationship predictions, most of the regulated and emerging DBPs, even at environmentally relevant low concentrations (sub-MIC levels), can induce oxidative stress, cause DNA damage, and activate DNA repair system [32,44]. Thus, they can potentially lead to antimicrobial resistance via sub-MIC selection pathways as previously discussed. Furthermore, DBPs can also be generated during the production and uses of food, pharmaceutical, and personal care products [31,45,46]. Therefore, attention should be paid on the effects that these DBPs and, especially the DBP mixtures, may have on the promotion of antimicrobial resistance. These effects need to be investigated at environmental concentrations (low sub-MIC levels). In addition to DBPs, the residual disinfectant and microbiome present in DWDSs may also significantly contribute to increase antimicrobial resistance in drinking water systems [9,29]. Finally, how the DBPs and disinfected drinking water impact human and animal gut microbiome and resistomes, therefore present an important cause of antimicrobial resistance development and pose health threats to immune-compromised individuals, is yet to be revealed. This may be an important factor for antimicrobial resistance development and hence pose health threats to immune-compromised individuals.

Conflict of interest statement

Nothing declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.coesh.2018.12.003.

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** of outstanding interest

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