





The application of non-oxidizing biocides to prevent biofouling in reverse osmosis polyamide membrane systems: a review

Luiz H. Da-Silva-Correa , Hayley Smith , Matthew C. Thibodeau, Bethany Welsh  and Heather L. Buckley* 

Department of Civil Engineering, Centre for Advanced Materials and Related Technologies (CAMTEC) and Institute for Integrated Energy System (IESVic), University of Victoria, Victoria, BC, Canada, V8P 5C2

*Corresponding author. E-mail: hbuckley@uvic.ca

 LHD-S, 0000-0003-3525-1929; HS, 0000-0001-6385-8037; BW, 0000-0001-9916-8396; HLB, 0000-0001-7147-0980

ABSTRACT

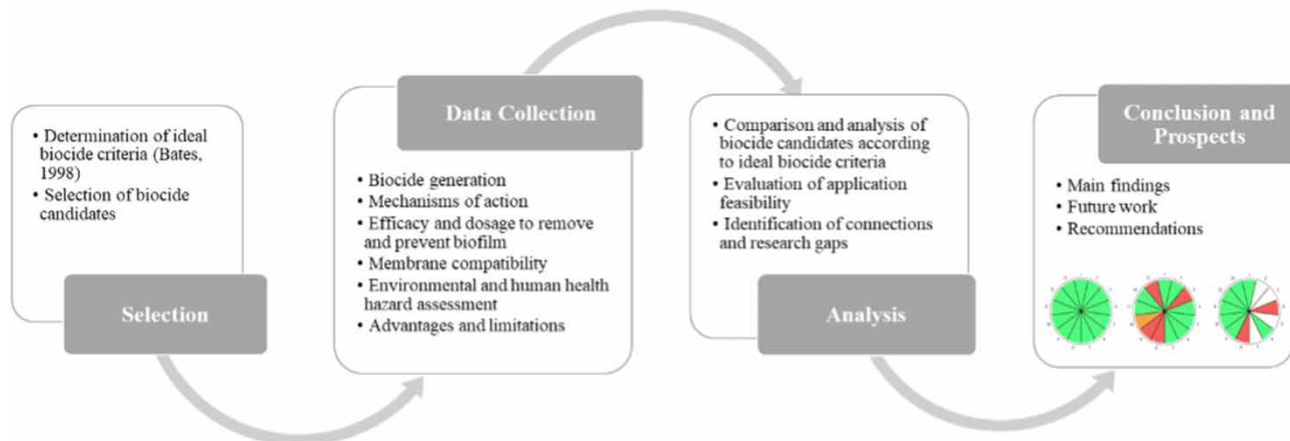
Biofouling of polyamide membranes is one of the main barriers faced by reverse osmosis (RO) technologies to supply fresh water. Currently, biofouling is addressed by feed water pretreatment using chlorine, followed by membrane cleaning. Chlorine damages polyamide membranes and also generates harmful disinfection byproducts. Thus, safer strategies are needed to prevent biofouling in polyamide membrane systems. This review investigates the applicability of the following non-oxidizing biocides in preventing and controlling biofouling in RO systems, including their antimicrobial efficiency, hazard levels, membrane compatibility, and applicability to drinking water treatment: (1) 2,2-dibromo-3-nitropropionamide (DBNPA); (2) 2-methyl-4-isothiazolin-3-one (MIT); (3) sodium bisulfite (SBS), (4) phenoxyethanol (PE), (5) sodium benzoate (SB). According to this review, MIT and DBNPA present most of the features attributed to an ideal anti-biofouling chemical but also are the most hazardous biocides. Due to safety and efficacy, none of the five chemicals were determined to be the final solution to address membrane biofouling. However, alternative RO biocide research is in early development and requires further investigation via biofouling prevention studies. Therefore, future research efforts on the investigation of economic, eco-friendly, and safe antifouling agents to prevent and treat biofouling in RO systems are paramount to promote sustainable water supply in water-stressed countries.

Key words: biocides, biofouling prevention, efficacy, polyamide membranes, reverse osmosis, safety, water treatment

HIGHLIGHTS

- An evaluation framework for anti-biofouling safety and efficacy is developed.
- DBNPA is a proficient model of biofouling prevention efficacy.
- MIT is a good model for antimicrobial efficacy, although not for safety.
- SBS is a reference for a membrane-compatible antimicrobial.
- PE and SB are good models for safety in biofouling prevention studies.

GRAPHICAL ABSTRACT



INTRODUCTION

Reverse osmosis technology background

Water scarcity can be defined as the lack of available freshwater resources to meet standard water demand and is one of the greatest challenges of this century (Arikrishnan & Rajendran 2021; Zhao *et al.* 2021). According to WHO (2017), 50–100 L of water per capita per day is needed to ensure the full realization of the right to water. Eke *et al.* (2020) reported that water scarcity is exacerbated by many factors, such as water pollution, climate change, population growth, and industrialization. According to UN-Water (2021), 2.3 billion people live in water-stressed countries, of which 733 million live in critically water-stressed countries. Clean water technologies such as membrane and thermal desalination may be applied to address several long-term potable water demands (Gude 2017; Singh *et al.* 2020; Singh 2021; Singh & Samsher 2021a, 2021b, 2021c; Van Vliet *et al.* 2021). Reverse osmosis (RO) polyamide membrane technology plays an essential role in addressing water scarcity due to its capability of producing freshwater from seawater, brackish water, and different types of wastewater (Kucera 2015; Zhao *et al.* 2021). The first documentation of RO polyamide membrane systems was in the 1760s (Kucera 2015). Eke *et al.* (2020) found that in 2020, 16,880 desalination plants were supplying freshwater with a total worldwide capacity of 97.2 million m³/day. Also, analyzing recent growth rates of the RO desalination market, Zhao *et al.* (2021) predicted that the total worldwide capacity of RO plants will double between 2015 and 2025.

Although membrane-based techniques are important to address water scarcity, membrane systems face many challenges, such as fouling, scaling, and membrane degradation (Kucera 2019; Zhao *et al.* 2021). One of the main difficulties in RO technologies is the biofouling of polyamide membranes (Nguyen *et al.* 2012; Kucera 2019; Zhao *et al.* 2021). Fazel & Darton (2001) investigated the membrane autopsies of 150 membranes used in RO applications from all over the world. The results showed that all membranes presented biofouling, of which 33% had biofouling as the main cause of systems failure. In a similar study, Pena *et al.* (2013) reported that 31.3% of 500 membranes presented severe biofouling causing the collapse of the membrane systems. The prevalence of this challenge makes the search for novel strategies to address biofouling in polyamide membrane systems necessary to promote sustainable water supply in water-stressed countries.

Biofilm

A biofilm is a complex structure of microorganisms that can include bacteria, fungi, algae, and extracellular polymeric substances (EPS). EPS is primarily composed of polysaccharides and proteins (Oh *et al.* 2018; Kucera 2019). Although the composition of a biofilm is dependent on temperature, pH, flow, osmotic pressure, and nutrient availability, approximately 90% of its mass is EPS and 10% is microorganisms (Nagaraja *et al.* 2017; Kucera 2019). Biofilms typically develop at solid and liquid interfaces and their formation is well characterized. The general steps of biofilm formation (Figure 1) are attachment, microcolony formation, maturation, and dispersion (Oh *et al.* 2018; Achinas *et al.* 2019). Bacteria secrete EPS, which helps additional bacteria to physically attach to the colony, protects them from antimicrobials, and enables the bacteria in the colony to communicate via molecular signals known as quorum sensing (Waters & Bassler 2005). Because

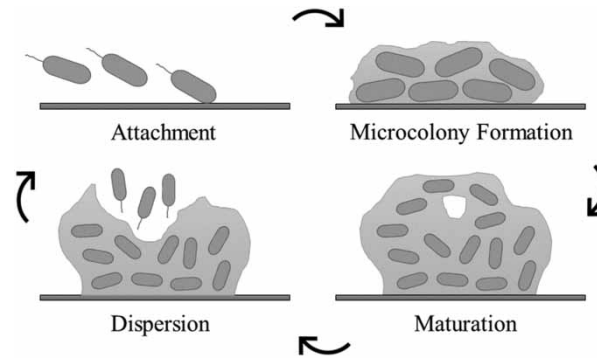


Figure 1 | Typical bacterial biofilm life cycle.

biofilms form readily, become resistant to antimicrobials, and are physically difficult to remove, they pose a challenge to membrane technologies.

Reverse osmosis biofouling

RO biofouling generally occurs when bacteria in the feed water enter the system and migrate to the membrane surface, where dissolved nutrients are concentrated due to concentration polarization (Dupont 2021). The design of the spiral wound elements and surface texture of the polyamide membrane create the ideal biofilm growth environment, perfect for attachment and accumulation of organisms (Dudley & Darton 1997). Microorganism concentrations as low as 1,000 CFU/mL can cause severe biofouling in membrane systems (Kucera 2015). Understanding the feed water composition is essential for preventing microbial growth. The source of feed water (brackish water, seawater, or potable water) impacts the growth conditions, influencing the types of microorganisms encountered including pioneer bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Zhang *et al.* 2006), which are known to initiate biofilms on membrane surfaces (Curtin 2020). Further, the concentration of contaminants in the water, such as total organic carbon (TOC) greater than 3 mg/L, can provide sufficient nutrients to promote bacterial build-up (Kucera 2015; Ras 2016). Ultimately, feed water dictates the biofouling potential of a membrane system, therefore pretreatment processes and bacteria mitigation through chemical or mechanical means are essential (Al-Ahmad *et al.* 2000; Kucera 2015).

Effects of biofouling on RO performance

Membrane biofilm formation significantly impacts the performance of RO systems and increases operational and treatment costs (Kucera 2015; Dupont 2021). Biofouling of RO membranes always results in an elevated pressure drop and a decrease in permeate flux (Ivnitsky *et al.* 2005; Kucera 2015). Pressure drop is the increase in pressure differential between the feed and concentrate lines and is a direct result of the pressure loss across the membrane due to friction by foulants (Al-Ahmad *et al.* 2000; Kucera 2015). Permeate flux is the volumetric flow rate of permeate produced over the membrane area (Kucera 2015). Permeate flux reduction and increased pressure differential are attributed to the increased resistance due to the low permeability of the membrane surface caused by the biofilm (Kramer & Tracey 1995; Abd El Aleem *et al.* 1998). Other adverse biofouling effects include the decline in permeate quality from membrane degradation, elevated feed pressure resulting in an increase in energy requirements, and shortened membrane lifespan due to additional cleaning treatments leading to degradation and biodegradation as a result of acidic byproducts from bacteria (Kramer & Tracey 1995; Abd El Aleem *et al.* 1998). Biofouling impacts on RO systems are summarized in Figure 2.

Techniques for monitoring and detection of biofouling in RO systems are implemented in water treatment operations to prevent biofouling impacts (Ras 2016). Monitoring practices include, but are not limited to, system performance analysis, frequent water sampling of feed water, permeate and concentrate quality, and physical inspection of the systems (Abd El Aleem *et al.* 1998). The biofouling indicators include a decrease in the permeate flow, stable salt rejection (percentage of influent compound retained by the RO membrane), and a large increase in differential pressure between the feed and concentrate across all stages of the RO elements (Kucera 2015).

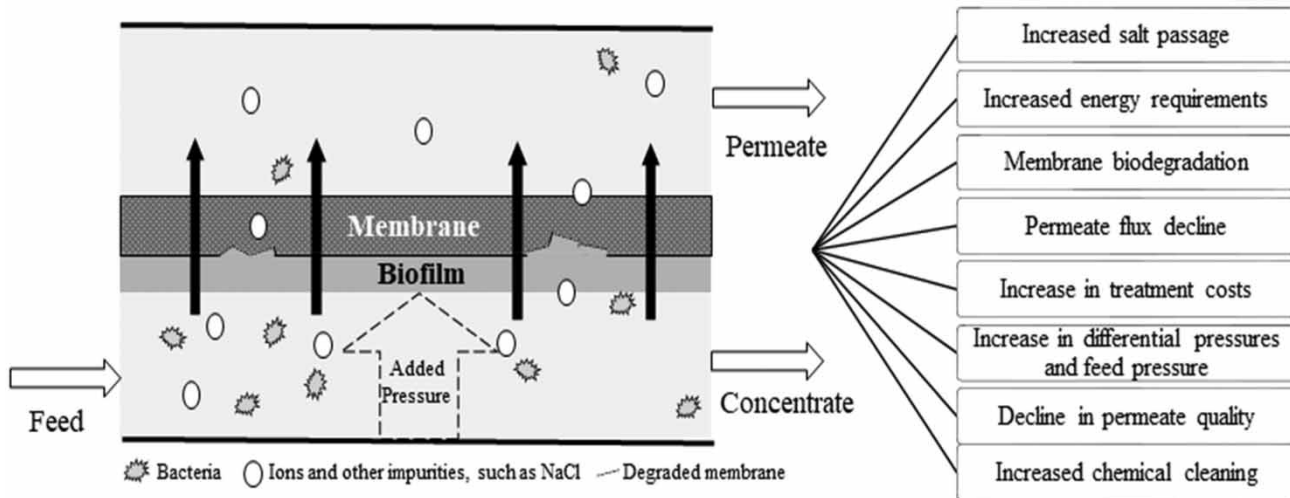


Figure 2 | Consequences of biofouling on RO systems (Kramer & Tracey 1995; Flemming 1997; Abd El Aleem *et al.* 1998; Baker & Dudley 1998; Nguyen *et al.* 2012; Kucera 2015; Kucera 2019).

Addressing biofouling in polyamide membrane systems: oxidizing biocide issues

There are several strategies to address biofouling in RO systems (Siddiqui *et al.* 2017). Kucera (2019) stated that these strategies may be based on membrane modification, membrane disinfection, membrane cleaning, and bacteria or nutrient modification. Currently, the effects of biofouling on the performance of RO systems are mainly handled by disinfection and cleaning techniques. Disinfection of polyamide membrane systems is performed via chemical (e.g. biocide treatment) or physical (e.g. ultraviolet radiation) methods with the objective of killing or disabling microorganisms in the system. Then, membrane cleaning is done to remove existing biofilms (Kucera 2019). RO systems are typically chemically disinfected by either shock dosing or continuously dosing biocides into the system. Continuous dosing is defined as maintaining a fixed concentration of the biocide in the feed stream of the water treatment process, whereas shock dosing is the intermittent addition of a biocide into the feed stream at higher concentrations and for a limited time (Bott 1998; Bertheas *et al.* 2009). Shock dosing is typically performed daily or weekly and can be applied on its own or in addition to continuous dosing. The aim of shock dosing is to remove any biofilm that has formed since the previous shock dose, while continuous dosing typically uses the minimum concentration of biocide necessary to maintain control of biofilm formation (Bott 1998; Grant & Bott 2005). Chlorine is the most common oxidizing biocide used to address biofouling of polyamide membrane systems and is applied during feed water pretreatment (chlorination) (Nguyen *et al.* 2012; Kucera 2019). This is because chemical feed water pretreatment with chlorine is effective against a wide range of microorganisms and promotes rapid cell death even at low concentrations (Kucera 2015). However, the application of chlorine in RO systems is limited by many factors since it damages polyamide membranes by oxidative degradation (Kim & Park 2015; Kucera 2015, 2019), it may form harmful and carcinogenic disinfection byproducts, such as halogenated contaminants, trihalomethanes, and haloacetic acids (Kim & Park 2015; Kucera 2015; Kucera 2019), and it is not safe to handle (Silva *et al.* 2020). Thus, due to the non-compatibility with polyamide membranes and corresponding hazards, chlorine has to be removed from the RO system after its application in the feed water pretreatment (dechlorination). Since free chlorine cannot be in direct contact with membranes, chlorine disinfection is only able to reduce or delay the biofouling of polyamide membranes (Kim & Park 2015; Siddiqui *et al.* 2017; Kucera 2019). Alternatively, non-oxidizing biocides can be applied in contact with polyamide membranes, thus the use of non-oxidizing anti-biofouling agents has been increasing in RO installations as an alternative to chlorine in many water treatment applications.

Biofilm prevention versus disinfection

It is important to note that disinfection and membrane cleaning techniques are only able to reduce or delay the effect of biofouling in membrane systems (Siddiqui *et al.* 2017). In order to find long-term sustainable solutions for biofouling, preventative treatments should be taken into consideration. Munla *et al.* (2012) showed that once formed, mature biofilms

can no longer be removed by shear force and the fouling is considered to be irreversible. This is because when forming biofilms, microorganisms release EPS, which holds the planktonic cells together and anchors them to the membrane surface. The EPS then becomes very difficult to remove without some sort of mechanical force, as the gel-like substance cross-links with the membrane surface and increases the mechanical stability of the biofilm (Nguyen *et al.* 2012). In addition, once microorganisms are established into a biofilm matrix, they display different properties and express different phenotypes than those in a planktonic state, leading to increased resistance to biocides (Bridier *et al.* 2011). According to Barraud *et al.* (2006), bacteria in biofilms can be 1,000-fold more resistant to antimicrobials than those in a planktonic state. On the grounds that the biofilm matrix consists of a structure that biocides generally cannot fully penetrate, bacteria in deeper layers of the biofilm are exposed to sub-lethal levels of the biocide, resulting in optimal conditions for biocidal tolerance development (Waters & Bassler 2005; Bridier *et al.* 2011). Ultimately, biofouling prevention (1) reduces the amount of irreversible fouling, (2) reduces the formation of more resistant variants of microorganisms, and (3) ultimately requires lower biocide dosing as compared to biofouling treatment. As a result, biofilm prevention techniques are preferred to promote sustainable water treatment by RO technologies.

Ideal biocide to address biofouling

Bates (1998) described the characteristics of an ideal biocide to prevent and reduce biofouling in polyamide membranes. The researcher identified that an ideal biocide should have the following characteristics: (1) the biocide should be compatible with polyamide membranes as well as all system components; (2) it should not pose hazards to human health and the environment; (3) the biocide should be effective against all types of microorganisms, be able to break up existing biofilms and disinfect the permeate side; (4) it needs to be biodegradable and inexpensive; and, (5) easy to handle, monitor, and inject into the membrane systems. Realistically, there is no current biocide available with all of these attributes (Kucera 2019). The fact that non-oxidizing biocides may potentially be applied in contact with polyamide membranes makes them promising candidates for long-term biofouling prevention studies. However, few studies were found in the literature that assesses the application of non-oxidizing biocides to prevent and reduce biofouling in RO polyamide membrane systems and consider all of these attributes (Siddiqui *et al.* 2017; Curtin 2020).

Aim and novelty of this paper


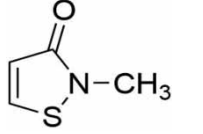
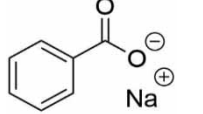
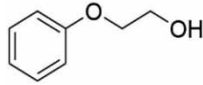
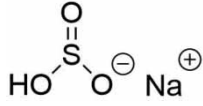
This paper intends to fill this research gap by reviewing the ability of five non-oxidizing biocides to prevent biofouling in polyamide membrane systems, considering all the attributes identified by Bates (1998), and promoting new, sustainable solutions to supply water via RO technologies. Specifically, this study presents a review on (a) the applicability of five non-oxidizing biocides in preventing and controlling biofouling in RO systems, (b) information on new non-oxidizing anti-biofouling agents under development stages, (c) a comprehensive discussion and analysis on the ability of these biocides to prevent and control biofouling in regards to the efficiency and feasibility for practical RO application, as well as (d) future research recommendations.

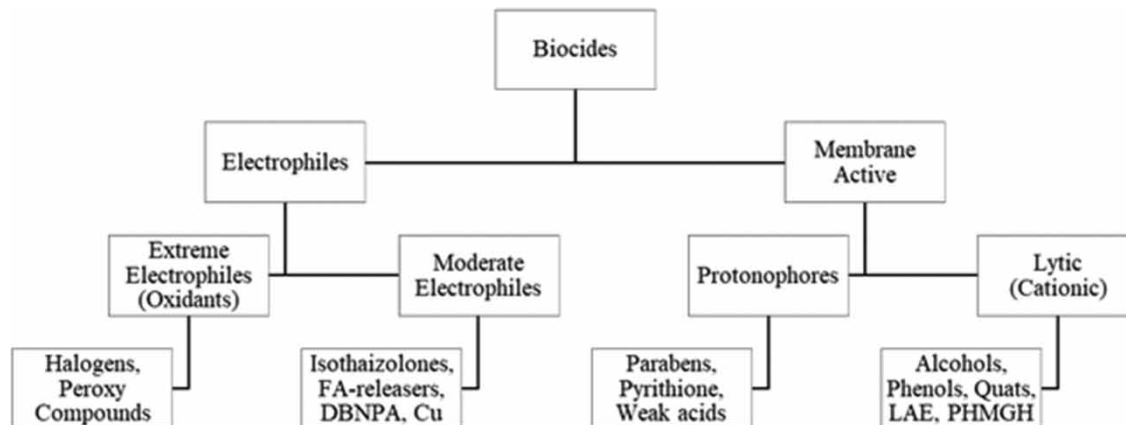
Biocides

Table 1 details the five non-oxidizing biocides that are discussed in this review. Three biocides are already applied in potable water applications: (1) 2,2-dibromo-3-nitropropionamide – DBNPA (off-line shock feed treatment), (2) 2-methyl-4-isothiazolin-3-one – MIT (off-line shock feed treatment and membrane cleaning), and (3) Sodium bisulfite – SBS (continuous on-line dechlorination-treatment and membrane storage) (Penna *et al.* 2002; Williams 2007; Kucera 2015, 2019; Siddiqui *et al.* 2017). Since the biocides are currently applied in polyamide membrane systems, they are recognized as reasonable candidates for biofouling prevention in RO systems. The two remaining biocides are commonly applied as preservatives in home and personal care products and were selected due to their low associated hazards: Phenoxyethanol (PE) and Sodium benzoate (SB) (CIR 2001; Buckley *et al.* 2017; Puschmann *et al.* 2018; Curtin 2020), making them interesting candidates for biofilm prevention and control.

Each biocide is evaluated on how well it meets the criteria described by Bates (1998), including efficacy in limiting biofilm formation on RO membranes, membrane compatibility, and relative hazards (Supplementary Material, Figure S1). The efficacy of each biocide is largely determined by its mechanism of action. According to Kucera (2019), biocides are characterized by their mechanism of action to kill microbiological cells or prevent growth. These groups include electrophiles, with sub-categories moderate and extreme (oxidants), or membrane-active, with sub-categories lytic and protonophores (Figure 3) (Chapman 2003). Electrophiles rapidly kill by entering the cell wall or by generating free radicals, which damage intracellular

Table 1 | Structural and chemical formulas of non-oxidizing biocides

Biocide	Name	CAS-number	Chemical formula	Structural formula
DBNPA	2,2-dibromo-3-nitropropionamide	10222-01-2	$C_3H_2Br_2N_2O$	
MIT	2-methyl-4-isothiazolin-3-one	2682-20-4	C_4H_5NOS	
SB	Sodium benzoate	532-32-1	$C_7H_5NaO_2$	
PE	Phenoxyethanol	122-99-6	$C_8H_{10}O_2$	
SBS	Sodium bisulfite	7631-90-5	$NaHSO_3$	

**Figure 3** | Mechanism of inactivation by biocides (Chapman 2003; Ferreira *et al.* 2009; Kim & Park 2016; Kucera 2019).

proteins, carbohydrates, lipids, and nucleic acids (Amjad 1993). The mechanism of action of membrane-active biocides is the disruption of the microorganism's cell membrane function and structure (HNGC 2015). The selection of the correct biocide depends on the type and number of bacteria present (Cloete *et al.* 1998). Biofilms can be composed of various bacteria species, such as fungus, algae, Gram-positive bacteria, Gram-negative bacteria, and yeast, so knowledge of organisms encountered is important (Cloete *et al.* 1998). Selecting incorrect biocides or dosages will result in an ineffective disinfection and is expensive (Cloete *et al.* 1998). The hazards posed by each biocide are determined from GreenScreen assessments of the chemicals, and other data collected from the literature (GSC 2021). All biocides are evaluated on their relative risk to the environment and to human health, including hazards to natural environments, human health after consumption (for cases of potable water treatment), and human health after handling the chemicals from an operational standpoint. With all of these attributes considered, the following sections discuss each of the five candidate non-oxidizing biocides and review their potential to prevent and remove biofouling in RO systems.

2,2-DIBROMO-3-NITRILOPROPIONAMIDE (DBNPA)

2,2-dibromo-3-nitrilopropionamide (DBNPA) is a halogenated amide and has been documented as an effective non-oxidizing biocide (Paulus 2005; Kucera 2019). In industry, DBNPA is widely used in water treatment, pulp, and paper but primarily in the oil industry to treat the water used to prepare fracturing fluids to control microbially induced corrosion of pipes (Paulus 2005; Campa *et al.* 2019). The application of DBNPA in RO systems is common due to its compatibility with polyamide membranes and fast biocidal response (Al-Juboori & Yusaf 2012; Kucera 2019). The use of DBNPA is prohibited from inline application for potable water production, due to the harmful toxicity of the hydrolysis byproducts (Blanchard *et al.* 1987; Baker & Dudley 1998; Bertheas *et al.* 2009). The typical membrane application is either by shock (intermittent) or continuous dosage and is not used for membrane storage because of the short half-life (Ras 2016; Kucera 2019). For instance, the hydrolysis half-life values at 25 °C at pH 6.7, 7.7, and 8.0 are 37, 5.8, and 2.0 hours, respectively (Exner *et al.* 1973). DBNPA acts rapidly on microorganisms, with a contact time of less than 1 h, and therefore the short half-life is generally not a concern for water treatment applications (Frayne 2001; HNGC 2015).

Generation

Generally, DBNPA is synthesized with the starting material cyanoacetamide (CAM) and prepared by acid-catalyzed bromination (Hesse 1896). Polyethylene glycol is the preferred solvent for DBNPA, providing good product stability and solubility (Wolf & Sterner 1972). DBNPA is soluble in water; however, the solution is only stable in the acidic pH range (Wolf & Sterner 1972). Therefore, DBNPA is generally available commercially as a 20% active solution in a water/polyethylene glycol blend (Eachus & Pohlman 2004; Kucera 2019). DBNPA must be stored in non-metal containers, due to incompatibility with metals (HNGC 2015; Kucera 2019). Moreover, exposure to sunlight (UV) can degrade DBNPA (Exner *et al.* 1973; Kucera 2019), significantly reducing the efficacy of the biocide.

Mechanisms of action

DBNPA is an example of a moderate electrophile. Collier *et al.* (1990) and Slawson *et al.* (1990) described electrophilic agents as biocides that react covalently with cellular nucleophiles to inactivate enzymes. Further, studies indicate that electrophiles initiate the formation of intracellular free radicals which contribute to their antimicrobial effects (Chapman & Diehl 1995; Kimura & Nishioka 1997). DBNPA acts by reacting with the sulfur-containing organic molecules in a bacterium cell such as glutathione or cysteine (Bucs *et al.* 2018). The reaction is irreversible, resulting in interruption of the transport of compounds, inhibiting the biological processes of the bacterium (Paulus 2005). In summary, DBNPA prevents biofouling rapidly, by permanently attacking the microbiological cell walls.

DBNPA has a broad spectrum of inactivation, effective at treating Gram-positive and Gram-negative bacteria, yeast, and fungi (Paulus 2005). However, DBNPA is not particularly effective against algae (Frayne 2001). Studies found in the literature indicated that DBNPA does not penetrate EPS (Schook *et al.* 2012; Siddiqui *et al.* 2017), and therefore DBNPA is not suitable for removing an established biofilm. For instance, Siddiqui *et al.* (2017) conducted a study investigating the prevention of biofilm growth and removal of established biofilms on RO membranes in a bench-top cross-flow system with high biofouling potential feed water. Results indicated the continuous DBNPA dosage achieved prevention of biofilm accumulation, displaying a reduction in pressure drop. In contrast, continuous dosage to an existing biofilm was not effective at removing EPS and inactive cells or restoring the pressure drop, showing DBNPA is not suitable for curative treatment. However, the DBNPA dosage was able to prevent further biofilm formation and a further increase in pressure drop (Siddiqui *et al.* 2017). The results of the study further confirm that the application of DBNPA is effective for preventing biofouling on RO and not suitable for removing existing biofilm.

Anti-biofouling effect: dosage and efficacy

In RO applications, DBNPA is typically applied directly to the feed water by continuous injection or shock treatment (Ras 2016; Kucera 2019). The dosage concentration depends on the feed water quality, including the biofouling potential and required permeate quality (Kucera 2010). A wide range of dosage intervals for continuous and shock injection are recommended, such as 2.5–10 mg/L for continuous treatment, or shock treatment at 10–30 mg/L for 1–3 h (Schook *et al.* 2012), every 2–7 days depending on microbial growth (Kucera 2010). Moreover, DBNPA should be applied to a clean membrane for the most effective application for biofouling prevention (Kucera 2019). The biocide is deactivated by reducing agents, so higher dosages are required in the presence of reducing agents, such as SBS (HNGC 2015). The application of

DBNPA to control biofouling is more efficient in oxidative conditions compared to reducing environments (Paulus 2005), and at pH lower than 8 (Schook *et al.* 2012). Degradation of DBNPA by hydrolysis increases significantly with increasing temperatures and pH (Exner *et al.* 1973).

Microbial efficacy and dosages of biocides are generally determined by microdilution antimicrobial susceptibility tests (Fane 2015; Curtin 2020; Curtin *et al.* 2021). The tests include the minimum inhibitory concentration (MIC), minimum biofilm eradication concentration (MBEC), minimum biofilm inhibitory concentration (MBIC), and minimum bactericidal concentration (MBC) (Curtin *et al.* 2021). According to Andrews (2001), MIC is acknowledged as the 'gold standard' for judging the antimicrobial susceptibility of organisms in the planktonic phase. The author defines MIC as the lowest concentration of a biocide to inhibit the visible growth of a microorganism after incubation overnight. Further, MIC values are used by universal diagnostic laboratories to confirm antimicrobial resistance and determine the *in vitro* activity of new biocides. The inhibitory values of the non-oxidizing biocides against *P. aeruginosa* and *S. aureus*, common pioneer organisms in membrane systems, for DBNPA and the other selected biocides are displayed in Table 2.

Membrane compatibility

Non-oxidizing biocides, including DBNPA, are commonly used for RO biofouling control since the chemicals can be applied directly to the RO elements without the concern of damaging the membranes (HNGC 2015; Majamaa *et al.* 2011). Kim & Park (2016) studied the membrane compatibility of DBNPA by completing a series of polyamide membrane destruction tests including morphological damage and oxidative damage assessments when contacted with the biocide for 24 h at high concentrations (1,000–100,000 mg/L). The study compared DBNPA to chlorine, an oxidizing biocide known to damage polyamide membranes. The researchers concluded that the polyamide surface layer was not damaged when treated with high concentrations of DBNPA, which confirms the industry practice of direct application of DBNPA on polyamide membranes.

Human and environmental health hazards

A summary of the human and environmental hazards levels is detailed in Tables 3 and 4. The hazard information for the biocides was collected from literature, including GreenScreen assessments and other data collected from Pharos (GSC 2021; Pharos 2021). The hazard levels are sourced from the Pharos database, which is based on the thresholds formed by the Globally Harmonized System of Classification and Labelling of Chemicals and additional benchmarks for endpoints by the U.S. EPA's Design for the Environment (Pharos 2021). The biocides with no hazard level data do not signify the absence of hazard, but an absence of studies in literature or low-confidence results.

DBNPA is a common treatment to prevent biofouling in RO for non-potable water applications (Al-Juboori & Yusaf 2012; Ras 2016). However, allowable applications are limited due to the chemical toxicity; DBNPA has been classed as an endocrine disruptor by the European Chemicals Agency (ECHA 2019). The application of DBNPA for potable water is prohibited, due to the passage (0.02%) of DBNPA into the permeate (Baker & Dudley 1998; Bertheas *et al.* 2009; Schook *et al.* 2012). In

Table 2 | Inhibitory concentrations of non-oxidizing biocides for *P. aeruginosa* and *S. aureus* (Biofilm pioneer microorganisms in RO systems)

Biocide	<i>P. aeruginosa</i>				<i>S. aureus</i>			
	MIC mg/L	MBEC	MBC	MBIC	MIC mg/L	MBEC	MBC	MBIC
DBNPA	80 ^a	–	80 ^a	–	160 ^a	–	160 ^a	–
MIT	30 ^b	78 ^b	–	22.5 ^b	45 ^c	–	–	–
SB	5,000 ^b	32,200 ^b	–	25,000 ^b	16,000 ^d	16,384 ^e	32,000 ^d	25,000 ^b
PE	48,000 ^f	120,000 ^b	–	36,000 ^b	1,590 ^b	–	3,180 ^g	–
SBS	780 ^h	–	–	–	512 ⁱ	–	512 ⁱ	–

Note: MIC, minimum inhibitory concentration; MBEC, minimum biofilm eradication concentration; MBC, minimum bactericidal concentration; MBIC, minimum biofilm inhibitory concentration. '–': inhibitory concentration was not found in the literature. MIC: The lowest concentration of an antimicrobial that inhibits visible growth of a planktonic culture after overnight incubation. MBEC: The lowest concentration at which biofilm density is reduced by >90% when compared to control OD values. MBC: The lowest concentration of an antimicrobial that achieves a 99.9% CFU reduction of the initial inoculum of planktonic cells. MBIC: Same as MBEC but the bacterial inoculation occurs with antibiotic exposure. (Macià *et al.* 2014; Wu *et al.* 2015; Curtin *et al.* 2021).

Source: ^aKim & Park (2015), ^bCurtin (2020), ^cLundov (2010), ^dWang *et al.* (2018), ^eGüven & Onurdağ (2014), ^fGillings (2010), ^gGrecka & Szweda (2021), ^hPenna *et al.* (2002) and ⁱFrank & Patel (2007).

Table 3 | Human hazard levels of non-oxidizing biocides

Biocides	Carcinogenicity	Neurotoxicity single exposure	Neurotoxicity repeated exposure	Skin sensitization	Respiratory sensitization	Eye irritation	Systemic toxicity single exposure	Systemic toxicity repeated exposure	Endocrine activity
DBNPA	Low ^a	Low ^b	Low ^c	High ^d	–	High ^d	Moderate ^a	–	High ^d
MIT	Low ^e	Moderate ^f	Low ^f	Very high ^e	Low ^f	Very high ^e	Moderate ^g	Moderate ^g	Low ^e
SB	Low ^e	Low ^h	Low ^h	Low ^e	Moderate ⁱ	Moderate ^e	Low ^h	Low ^h	Low ^e
PE	Low ^j	Moderate ^k	Low ^k	Low ^k	–	High ^k	–	Low ^k	–
SBS	Low ^m	–	–	High ⁿ	High ⁿ	High ^o	–	–	–

Hazard levels: very low, low, moderate, high, very high. '–': data gap.

Source: ^aZheng *et al.* (2021), ^bMin *et al.* (2019), ^cChen (2012), ^dECHA (2019), ^eCanavez *et al.* (2021), ^fBurnett *et al.* (2010), ^gKim & Choi (2019), ^hCIR (2001), ⁱSCCP (2005), ^jJBRC (2007), ^kECHA (2015), ^mEFSA ANS Panel (2016), ⁿVally *et al.* (2009) and ^oWalls *et al.* (2018).

Table 4 | Environmental health hazard levels of non-oxidizing biocides

Biocides	Acute mammalian toxicity	Acute aquatic toxicity	Terrestrial ecotoxicity	Bioaccumulation	Chronic aquatic toxicity	Persistence
DBNPA	Very high ^a	Very high ^b	–	–	–	–
MIT	Very high ^c	Very high ^d	Moderate ^c	Very low ^e	Very high ^d	Low ^e
SB	Low ^g	Low ^g	Moderate ^g	Low ^g	Low ^g	Low ^g
PE	Moderate ^{f,h}	Low ^h	–	Very low ^h	Low ^h	Very low ^h
SBS	Low ⁱ	Moderate ^j	–	Very low ⁱ	–	Low ^k

Hazard levels: very low, low, moderate, high, very high. '–': data gap.

Source: ^aAlexander *et al.* (2001), ^bChen (2012), ^cBurnett *et al.* (2010), ^dVan Huizen *et al.* (2017), ^eSilva *et al.* (2020), ^fUNEP (2004), ^gWHO (2000), ^hECHA (2015), ⁱEFSA ANS Panel (2016), ^jRyon *et al.* (2002) and ^kBaker & Dudley (1998).

addition, appropriate measures and risk management are required for handling DBNPA because the biocide is harmful by acute exposure by oral or inhalation pathways and is a skin irritant, skin sensitizer, and causes eye damage (ECHA 2019).

When DBNPA is applied to aqueous solutions, such as RO systems, hydrolysis occurs easily due to the short half-life (Ras 2016). There are two known hydrolysis pathways of DBNPA. The primary degradation products by hydrolysis are dibromoacetamide (DBAM), dibromoacetic acid, and dibromoacetoneitrile (DBAN) (Exner *et al.* 1973; Blanchard *et al.* 1987). Hydrolysis ends with oxalic acid which oxidizes slowly to CO₂ (Paulus 2005). Dibromoacetic acid is more persistent in the environment with a half-life of 300 days (Exner *et al.* 1973), and DBAN is three times more toxic than DBNPA, with LC₅₀ values for DBAN of 0.55 mg/L and DBNPA of 1.8 mg/L (Mayes *et al.* 1985; Blanchard *et al.* 1987). Due to the harmful degradation products of DBNPA, there is a concern for human and environmental impacts when DBNPA is applied to water systems. A secondary degradation pathway of DBNPA occurs when there is a high ratio of TOC to dose of DBNPA. DBNPA degrades to monobromonitropropionamide (MBNPA) and CAM, where MBNPA is two times less toxic compared to DBNPA, with the LC₅₀ value of MBNPA as 3.4 mg/L (Mayes *et al.* 1985; Blanchard *et al.* 1987).

To further understand the aquatic toxicology of DBNPA, Chen (2012) evaluated the chronic toxicity of the chemical in *Daphnia magna* and rainbow trout. The researcher evaluated long-term exposure at relatively low concentrations of DBNPA, ranging from 0.005 to 0.3 ppm and 14–28 days, depending on species. The author concluded that DBNPA affected the reproduction and survival of *Daphnia magna* at concentrations starting at 0.053 ppm, and DBNPA affected the growth of juvenile rainbow trout at a concentration starting at 0.018 ppm after 28 days of exposure. This study showed preliminary evidence that DBNPA has negative impacts on aquatic life (Chen 2012). Overall, proper risk assessment and chemical management are essential when applying DBNPA to water systems.

Advantages and limitations

One of the major limitations for DBNPA as a biocide is that it is not effective at removing biofilms from polyamide membranes (Siddiqui *et al.* 2017). This is because DBNPA is only capable of preventing biofouling as it does not penetrate

EPS and is most effective when applied on clean membranes (Schook *et al.* 2012; Kucera 2019). Also, DBNPA must be used off-line for potable water or food and beverage applications (Kucera 2019), due to health hazard concerns of DBNPA and the harmful hydrolysis degradation products, DBAN and DBAM (Supplementary Material, Tables S1 and S2) (Exner *et al.* 1973; Blanchard *et al.* 1987). DBNPA is very soluble in water, with a water solubility of 15 g/L at 20 °C (Wolf & Sterner 1972) and degrades easily due to a short half-life. DBNPA half-life decreases with increased pH, which impacts product stability and the ease of storage and transportation (Al-Juboori & Yusaf 2012). However, the half-life is generally not an issue for preventing biofouling since the biocidal action occurs rapidly before hydrolysis making DBNPA an advantageous biocide for shock or continuous dosage for RO, but not effective for membrane storage (Frayne 2001; HNGC 2015; Ras 2016). Continuous injection can be more expensive in terms of treatment costs, so shock dosages are typically applied (HNGC 2015; Ras 2016; Kucera 2019). However, the relatively low concentration required for shock dosages provides a more economic biofouling prevention treatment when compared to other biocides. Overall, DBNPA is beneficial for RO membrane application due to the fast-acting and effective prevention treatment at low concentrations and compatibility with polyamide membranes (HNGC 2015; Ras 2016; Kucera 2019).

METHYLISOTHIAZOLINONE (MIT)

2-methyl-4-isothiazolin-3-one (MIT) is a heterocyclic organosulfur compound commonly used in cooling system applications, industrial water treatment, cosmetics, and daily life products (such as detergents and paints) due to its wide-spectrum biocidal efficacy against bacteria, fungi, and algae (Frayne 2001; Williams & McGinley 2010; Majamaa *et al.* 2011; Silva *et al.* 2020). MIT is applied in RO applications as a non-oxidizing biocide in cleaning events and membrane storage either alone or in combination with 5-chloro-2-methyl-4-isothiazolin-3-one (CMIT) in a CMIT/MIT ratio of 3:1 (Collier *et al.* 1990; Majamaa *et al.* 2011; Kucera 2015; Li *et al.* 2016). According to Kucera (2015), isothiazolinones are a viable choice to control biofouling in polyamide membrane systems. However, although MIT applications as a non-oxidizing biocide are known to be effective in various industrial settings, most of the reports found in the literature were focused on biofouling mitigation by MIT treatment and few studies were found on its capability in preventing biofouling in RO membrane-based water treatment systems. In other words, although MIT is widely applied in RO installations, its application for biofouling prevention is not sufficiently studied.

Generation

The first synthesis of MIT was reported in the 1760s (Crow & Leonard 1964). In this process, MIT was produced through the cyclization of *cis-N*-methyl-3-thiocyanatoacrylamide with an overall yield of 80% (Silva *et al.* 2020). Currently, MIT is synthesized via the cyclization of amides that are produced from carboxylic acids (Silva *et al.* 2020). The popularization of the mixture of MIT and CMIT as biocides in the RO industry occurred in the late 1980s (Collier *et al.* 1990). One of the most commonly used CMIT/MIT biocides available today is marketed under the Kathon™ brand (Frayne 2001; Majamaa *et al.* 2011; Park & Kwon 2016; Daulisio & Schneider 2020). The mixture of isothiazolinones is usually marketed at an active concentration of 1.5% (1.15% of CMIT and 0.35% of MIT) (Frayne 2001; Kim *et al.* 2019; Daulisio & Schneider 2020). Although the CMIT/MIT mixture is frequently used in RO applications, the most recent isothiazolinone biocide applications in water treatment have been based on products containing MIT as the only active ingredient (Williams & McGinley 2010; Wang *et al.* 2020; Zeng *et al.* 2020). This is because treatment and disposal of the RO concentrate resulting from a CMIT/MIT biocide treatment are very expensive, probably due to the high toxicity of CMIT, which is approximately one hundred times more toxic than MIT (Williams & McGinley 2010; Silva *et al.* 2020).

Mechanisms of action

MIT is a moderate electrophile that can enter the cell membrane by diffusion or active cell transport (Kucera 2019; Silva *et al.* 2020). The mechanisms of action of MIT rapidly inhibit bacteria growth by impairing microbial respiration and energy production (ATP synthesis) followed by a slow cell death due to the inactivation of enzymes and irreversible cell damage by free radicals (Frayne 2001; Williams 2006; Kucera 2019; Silva *et al.* 2020). Within the cell, the electron-deficient N–S bond of isothiazolinone reacts with nucleophilic groups, such as thiols present in the active sites of many enzymes and in proteins, inhibiting enzymatic activity. The nucleophilic reactions between MIT and thiol-containing compounds impair microbial respiration, energy production, and other microbial functions causing growth inhibition and cellular death (Collier *et al.* 1990; Williams 2006; Kucera 2019; Silva *et al.* 2020). Microbial growth inhibition usually takes a few minutes and the cell death

might take several hours (Morley *et al.* 2005; Kucera 2019; Silva *et al.* 2020). The slow kinetics of inactivation can be overcome by increasing the biocide concentration or adding surfactants (Kucera 2019; Liu *et al.* 2020).

Notably, MIT presents high antimicrobial efficacy against a wide range of microorganisms, such as bacteria, algae, and fungi (Williams 2006; Majamaa *et al.* 2011; Kucera 2015). According to Frayne (2001), this antifoulant has optimal biocidal efficacy against aerobic and spore-forming bacteria at pH 6.5–9. Furthermore, Frayne (2001), indicates that MIT performs best as a fungicide and an algicide under acidic-to-slightly-alkaline pH levels. These pH ranges match the operational conditions of polyamide membrane systems, making the application of MIT as an anti-biofouling agent suitable for RO systems. Williams (2006), in a study on the mechanism of action of industrial isothiazolinone biocides in water treatment applications, concluded that it is very difficult for microorganisms to build up resistance to MIT because the mechanism of action results in a wide spectrum of inhibitory pathways. In the RO industry, MIT is frequently applied for both membrane storage and cleaning. This indicates that this chemical cannot only inhibit microbial growth but also it can remove mature biofilms by disrupting the EPS matrix of the biofilm (Kucera 2015; Kucera 2019; Liu *et al.* 2020). Therefore, MIT is capable of preventing and controlling the biofouling of polyamide membranes.

Anti-biofouling effect: dosage and efficacy

Isothiazolones are applied in RO off-line operations for drinking water treatments at dosage rates ranging from 50 to 120 ppm (1.5% active isothiazoline) with an exposure time of 5–6 h (Frayne 2001; Williams 2007; Kucera 2019). According to Kucera (2019), the high dosages and long contact period recommended for biofouling control by MIT treatment make its application less attractive for on-line or shock treatments. Williams (2007) performed various MIC studies on the antimicrobial efficacy of MIT against different microbial groups using standard MIC protocols. The experiments also covered a broad range of conditions, such as pH 5–8, temperatures of 24–35 °C, media (complex and defined), and incubation periods (1–7 days). The authors concluded that MIT is a highly effective biocide. The researchers also reported that MIT maintains an excellent antimicrobial efficiency against different types of microorganisms and physical stability in wide pH (2–10) and temperature (5–60 °C) ranges. This conclusion is supported by subsequent literature (Majamaa *et al.* 2011; Park & Kwon 2016; Silva *et al.* 2020).

Although MIT is already widely applied to biofouling control in RO systems, there are no laboratory-scale or pilot-scale studies on RO membrane-based water treatment system units in the literature regarding the application of MIT to prevent biofouling of polyamide membranes. However, Curtin *et al.* (2021) tested the efficacy of MIT, SB, and PE in preventing and removing single-species static biofilm formation in a 96-well plates experiment using *Pseudomonas aeruginosa* (a common biofilm former in RO systems) with a final cell concentration of 1×10^6 CFU/mL. To assess the antimicrobial efficacy of these biocides, minimum biofilm eradication concentrations (MBEC) and MBIC were determined based on a relative fluorescence analysis (LIVE/DEAD BacLight staining method). The experiments were performed at 37 °C for 24 h. In the biofilm removal experiments, the plates contained the highest concentrations of MIT, PE, SB of 600 mg/L, 960,000 mg/L, and 250,000 mg/L, respectively, while in the biofilm prevention tests, the highest concentrations were three-quarters of these concentrations. The results indicated that MIT presented lower inhibitory concentrations as compared to SB and PE (Table 2). The researchers concluded that MIT was the most effective of the three biocides in removing and preventing biofilm, showing it to be a good model compound as a reference for biocide efficacy in RO studies.

Membrane compatibility

Isothiazolinone biocides such as MIT are inherently biodegradable into less hazardous compounds, inexpensive, and compatible with polyamide membranes as well as all RO system compartments (Majamaa *et al.* 2011; Kucera 2015, 2019). Majamaa *et al.* (2011) performed long-term membrane compatibility tests with both new and used brackish water polyamide membranes at different temperatures (25 and 40 °C). In this study, Majamaa *et al.* (2011) compared the membrane compatibility of a CMIT/MIT mixture with DBNPA and sodium metabisulphite (the current standard chemical used for polyamide membrane preservation and storage) at active dosage concentrations of 10 mg/L, 30 mg/L, and 3,900 mg/L, respectively. The performance of the membranes was assessed on salt rejection, transmembrane pressure drop, and permeate flow after membrane storage periods of 1, 3, 6, and 12 months. The researchers concluded that both CMIT/MIT and DBNPA were compatible with polyamide membranes and their application to replace sodium metabisulphite is economically feasible with CMIT/MIT being the most economical option. Furthermore, the membrane performance results showed that CMIT/

MIT and DBNPA could control microbial growth during all membrane storage periods (Majamaa *et al.* 2011; Kucera 2019). Hence, MIT is compatible with polyamide membranes (Williams 2007; Kucera 2015, 2019; Majamaa *et al.* 2011).

Human and environmental health hazards

Despite presenting remarkable biocidal efficacy in controlling biofouling in RO applications, isothiazolinones are skin sensitizers, eye irritants, ecotoxic, and allergy triggers (Frayne 2001; Willi *et al.* 2011; Kucera 2019; Curtin 2020; Silva *et al.* 2020; Curtin *et al.* 2021); thus, careful handling is required (Willi *et al.* 2011; Kucera 2019; Silva *et al.* 2020). In a literature review on the toxicity profiles of isothiazolinone biocides, Silva *et al.* (2020) pointed out that isothiazolinone biocides present potential health hazards for industrial workers and final product users. Maximum permitted concentrations of CMIT/MIT biocides and MIT biocides in cosmetics (direct human exposure) are 15 and 100 mg/L, respectively (Aerts *et al.* 2017; Silva *et al.* 2020). Workers exposed to higher CMIT/MIT concentrations (>100 mg/L) may experience harmful effects. For instance, Willi *et al.* (2011), in a case study on health effects of handling isothiazolinone biocides in industrial settings, reported severe skin irritation followed by allergic dermatitis of an industrial worker after handling a 3:1 ratio CMIT/MIT biocide (product concentration of 100 mg/L) applied to control biofouling in a cooling tower. Besides skin irritation and allergies, human exposure to isothiazolinone biocides might cause respiratory problems (Bourke *et al.* 1997; Lee *et al.* 2018; Silva *et al.* 2020). Regarding the carcinogenic risk of MIT, recent studies show that MIT is not carcinogenic (Burnett *et al.* 2010; Kim *et al.* 2019; Canavez *et al.* 2021). Kim *et al.* (2019) assessed the potential risks to human health of the CMIT/MIT biocide (Kathon™ brand). The authors reported that the CMIT/MIT biocide (30–300 mg/L) presented no evidence of carcinogenic effects in a 24-month drinking water study in rats. The researchers also reported that the Kathon biocide (400 mg/L) did not present dermal carcinogenic effects in mice in a 30 months experiment. Similar results were reported by Burnett *et al.* (2010) and Canavez *et al.* (2021).

Along with human hazards, the application of isothiazolinone biocides may pose environmental health hazards (Wang *et al.* 2019; Silva *et al.* 2020). In an extensive literature review on the safety assessment of MIT, Burnett *et al.* (2010) reported many acute mammalian studies which indicated that MIT may be lethal if inhaled or ingested. For instance, an acute oral study showed that the median lethal doses (LD50) for male and female rats were 274.6 mg and 105.7 mg/kg of body weight, respectively (Burnett *et al.* 2010). Aquatic toxicity studies showed that MIT is very toxic to aquatic life (Santos *et al.* 2016; Van Huizen *et al.* 2017; Kucera 2019). Van Huizen *et al.* (2017) investigated the effects of MIT exposure on five different planarian species, which are common flatworms found in freshwater streams, lakes, ponds, and rivers. The researchers found that MIT concentrations higher than 4.5 mg/L are lethal to planarians. It also was noted that planarians exposed to MIT concentrations of approximately 1.7 mg/L presented neuromuscular and epithelial-integrity defects. Furthermore, Santos *et al.* (2016) assessed the effect of MIT exposure on *Xenopus laevis* embryos and tadpoles (the South African clawed frog) wound healing and tail regeneration to investigate the adverse effects of MIT on aquatic animals. The authors concluded that exposure to MIT impairs tissue regeneration and wound repair in *Xenopus laevis* which may lead to lethality. In contrast to these studies, a review by Silva *et al.* (2020) indicated that MIT is not likely to cause long-term ecological disturbances in aquatic and terrestrial environments because MIT will not persist in the environment due to its rapid biological and chemical degradation, as well as its diversified modes and rates of dissipation and degradation. The authors also reported that in several environmental systems, the degradation of MIT will lead to malonamic, malonic, acetic, and formic acids which will be ultimately converted to CO₂ (Supplementary Material, Tables S1 and S2).

Advantages and limitations

The main limitations of MIT biocide treatment are its high toxicity and the long exposure time and high doses needed for controlling biofouling (Li *et al.* 2016; Kucera 2019; Silva *et al.* 2020). Silva *et al.* (2020) reported many hazards associated with the industrial use of MIT as a biocide such as high aquatic toxicity and adverse health effects (e.g. eye and skin irritation). Li *et al.* (2016) reported that the concentrate containing MIT is not easily and safely disposable, because MIT needs to be removed from the concentrate as a result of its high toxicity. The researchers also reported that UV radiation and ozonation can both degrade MIT, providing a possible post-treatment approach for both the concentrate and permeate. However, this would increase the already high operational cost associated with RO systems. Due to these limitations, Kucera (2019) indicated that MIT might not be ideal for on-line potable water applications.

The main advantages of MIT as an industrial biocide rely on its excellent antimicrobial efficacy, compatibility with polyamide membranes, and distinguished biocidal performance in a good range of conditions (Williams 2007; Majamaa *et al.*

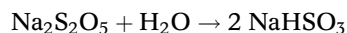
2011; Kucera 2019). Further, MIT is cost-competitive and very difficult to present microbial resistance (Majamaa *et al.* 2011; Kucera 2019). Rapid degradation means that it is unlikely to pose a long-term threat to environmental health (Williams 2007). According to Kucera (2019), MIT treatment presents an excellent performance in preventing microbial growth in long-term membrane storage. In addition, MIT is completely soluble in water which facilitates its injection in water treatment applications (Burnett *et al.* 2010). However, more studies need to be done to investigate long-term continuous MIT application for biofouling prevention in RO systems.

SODIUM BISULFITE

Sodium bisulfite is an inorganic salt, commercially used as a reducing agent in cosmetics, and as a preservative in a variety of food products and pharmaceuticals (Nair *et al.* 2003; Macedo *et al.* 2019; Ohara *et al.* 2020). In industrial water treatment applications, SBS is regularly dosed as the reducing agent after chlorine disinfection to remove free chlorine from the system and is widely used as a preservative during long-term membrane storage (Penna *et al.* 2002; Kucera 2019). The biocide has also been dosed to protect pipelines from microbially influenced corrosion and as a quenching compound to remove ozone from drinking water treatment trains (Park *et al.* 2011; Kucera 2019). Other applications include the preservation of water softeners and dechlorinating carbon bed filters (Penna *et al.* 2002). Most SBS solutions are about 33–37% active (Kucera 2019). Due to its varied applications in water treatment systems, antimicrobial properties, and its comparatively low risk to the environment, SBS may be suitable to use as a preventative biocide in RO systems.

Generation

As per the following chemical reaction, SBS is formed when sodium metabisulfite (SMBS), a decomposable, white powder, is dissolved in water (Redondo & Lomax 2001).



Since SMBS is readily soluble in water (3,000 g/L in water at 20 °C, according to Ough & Were (2005)), the compounds may be considered functionally equivalent in water treatment applications. Both compounds are regularly used as preservatives and gradually oxidize and turn into sulfate due to the loss of sulfur dioxide when exposed to air (EFSA ANS Panel 2016). In solution, SBS speciates into sulfite di-anions (SO_3^{2-}), bisulfite anions (HSO_3^-), sulfurous acid (H_2SO_3), and sulfur dioxide (SO_2), in proportions dependent on pH (Roberts *et al.* 2012). In a 10% aqueous solution of SBS, the pH range of 2.5–5.5 favors the production of sulfurous acid (EFSA ANS Panel 2016). Solid SMBS has a typical shelf life of 4–6 months under cool, dry storage conditions (Dow 2011). A typical solution life of SBS varies with concentration. At 100,000, 200,000, and 300,000 ppm, the solution life of SBS is 1 week, 1 month, and 6 months, respectively (Dow 2011).

Mechanisms of action

At higher concentrations, SBS can be used as a non-oxidizing antimicrobial with a relatively simple mechanism of action. SBS scavenges oxygen, effectively removing it from the surrounding environment and killing aerobic bacteria (Feiner 2006; HNGC 2015). SBS is a cell membrane-active biocide; its strong bactericidal effect comes from inhibiting key enzymes in microorganisms, such as those involved in energy production (ATP synthesis) and bacterial metabolism (Irwin *et al.* 2017; Ohara *et al.* 2020). Due to its oxygen scavenging potential, the addition of SBS effectively controls aerobic bacterial growth but simultaneously creates an environment where anaerobic bacteria can proliferate (Kucera 2019). Additionally, Baker & Dudley (1998) reported that SBS would be ineffective against bacteria that can adapt to anaerobic conditions, such as sulphate-reducing bacteria. SBS is described as having a bacteriostatic effect, since it prevents biological growth but does not remove existing bacteria (Kucera 2019). As a result, SBS will not be effective on mature biofilms or EPS and is only effective in feed water that has a low potential for fouling. Ohara *et al.* (2020) reported that SBS had a strong bactericidal effect at pH 4.6. This is supported by other studies which concluded the efficacy of SBS increased in acidic conditions (Penna *et al.* 2002; Ryon *et al.* 2002; Murano *et al.* 2005). The effect of temperature on the efficacy of SBS was not found in the literature.

Anti-biofouling effect: dosage and efficacy

Sodium bisulfite is commonly used to limit microbial growth in RO systems through shock dosing and is used as the chemical additive for inhibiting biological growth during membrane storage (Redondo & Lomax 2001; Kucera 2019). For shocking dosing, 500–1,000 mg/L, or 0.05–0.1 wt% of SBS is dosed in the feed line for 30 min (Dow 2011; Wei *et al.* 2012; Kucera

2019). Shock treatment is carried out every 24 h, or when microbial growth is suspected, in order to control aerobic bacteria (Dow 2011). An SBS solution of 0.1–1% concentration is used to inhibit biofouling during membrane storage (Penna *et al.* 2002; Wei *et al.* 2012; Kucera 2019). Redondo & Lomax (2001) reported that continuous dosing of up to 50 ppm SBS in the feed stream of RO plants was effective in controlling biological fouling, although this was in low-to medium-fouling potential seawater.

Baker & Dudley (1998) reported on the efficacy of shock dosing SBS as a biocide, stating that after 4 h of exposure at 500 ppm of SBS, there was a 75% kill noted for aerobic marine bacteria. Alternatively, other data indicated kill rates of up to 99% for seawater microflora at a concentration of 500 ppm SBS with a contact time of 30 min (Baker & Dudley 1998). A study by Murano *et al.* (2005), on the bactericidal effects of SBS at varying acidic conditions, reported that SBS did not affect the viability of the target organism (*H. pylori*) at neutral pH (7.0) and was more effective at a lower pH. While studying the effects of SBS on pathogenic microorganisms in catheter lumens, Ohara *et al.* (2020) confirmed that, at a low pH, SBS has an evident bactericidal effect against both *P. aeruginosa* and *S. aureus*. For SBS in particular, the type of microorganism present in the feed water will have a significant effect on its relative efficacy. Although SBS is effective at controlling aerobic bacteria, it creates an ideal environment for anaerobic bacteria and can be ineffective against sulfate-reducing bacteria which are able to adapt to anaerobic conditions (Baker & Dudley 1998). Penna *et al.* (2002) listed the lowest concentration of SBS which prevents visible growth of *P. aeruginosa*, or the MIC, as 780 mg/L. The MIC and MBC of SBS found for *S. aureus* was 512 mg/L. The MBEC and MBIC for either target microorganism were not found in the literature (Table 2).

Concentrations of SBS used for shock dosing and long-term storage of membranes have been largely accepted as industry standards; however, the results presented by Baker & Dudley (1998) indicate the questionable efficacy of shock dosing SBS. SBS has been shown to have a strong bactericidal effect on planktonic cells and is a widely used preservative for relatively clean membranes during long-term storage, although it is not effective against existing biofilms or anaerobic bacteria.

Membrane compatibility

The compatibility of SBS with RO membranes and overall system components is confirmed by the regular use of the biocide as a preservative during long-term RO membrane storage, application as an agent in membrane feed water pretreatment, and common use in a variety of other water treatment processes. Wei *et al.* (2012) studied the effects of polysulfone ultrafiltration membrane surface modification by the preadsorption of SBS and found that it improved membrane antifouling properties while increasing flux and salt rejection. No reports were found in the literature as to whether the same effects would be seen with the adsorption of SBS on polyamide membranes.

Feed water quality should be carefully monitored to ensure compatibility with the proposed biocide. In cases where the feed water results in the RO membrane being fouled with heavy metals, SBS will partially convert to oxidants, resulting in membrane degradation (Dow 2011). If chlorine and SBS are being dosed consecutively in the treatment process, the SBS injection point may lead to an increase in anaerobic biological growth. In combination with chlorination, Hoeck (2017) noted a decrease in RO membrane biofouling potential when the SBS injection point was placed between dual media filters and cartridge filters, and biofouling potential increased as the injection point moved closer to the RO membranes. During membrane storage, SBS scavenges oxygen from the air, producing sodium sulfate and causing a decrease in pH (Kucera 2019). It is recommended to periodically change the bisulfite solution during membrane storage in order to control changes in pH so as to not lead to membrane degradation. During RO applications, the process pH after the addition of SBS should be carefully monitored in order to avoid membrane degradation. Additionally, feed water should be analyzed for heavy metals, which can react with dissolved SBS and foul the membrane. Overall, as evidenced by its wide use as a preservative during membrane storage and common application in membrane feed water pretreatment, SBS is very compatible with polyamide membranes in most cases.

Human and environmental health hazards

It is widely accepted that SBS in small doses is a relatively low-hazard antimicrobial, evident from its varied use in food, cosmetics, and pharmaceutical products. However, concentrated solutions are irritating to the skin, eyes, and mucous membranes, and even low doses may cause adverse reactions to individuals with sulfite allergies (Budavari *et al.* 1989; Kolaei *et al.* 2012). Many studies have recognized sensitivity to sulfites in some individuals and reported adverse effects after topical and oral exposure, ranging from asthma, dermatitis, and rhinoconjunctivitis to life-threatening anaphylactic

and asthmatic reactions (Vally *et al.* 2009; García-Gavín *et al.* 2012; Oliphant *et al.* 2012). At a neutral pH, a large portion of aqueous SBS will be composed of the sulfite dianion, which is considered to be responsible for the skin sensitization potency of SBS (Roberts *et al.* 2012). As such, SBS requires careful handling since it can pose a high human hazard to individuals who are sensitive to the compound.

In drinking water applications, overdosing SBS may lead to higher levels of the biocide in distributed water, potentially causing human health concerns. The bactericidal effect of SBS on beneficial bacteria in the human digestive system was studied by Irwin *et al.* (2017), concluding that 2 h of exposure to sulfite concentrations between 250 and 500 ppm could substantially alter the gut and/or mouth microbiome. In RO applications, overdosing SBS may pose an environmental hazard as excess levels of SBS in either the concentrate or permeate will scavenge oxygen when distributed to receiving waters. The environmental hazard of SBS was reported by Ryon *et al.* (2002), who studied the impact on streams from the use of SBS as a dechlorinating agent. The study concluded that inaccurate dosing or overfeed of SBS can create an excess of sulfite in receiving waters, potentially leading to decreases in pH and dissolved oxygen, and causing mortality in fish. As a result, according to Redondo & Lomax (2001), during shock treatments when the permeate contains 1–4% of the concentration of SBS in the feed water, an assessment of the permeate quality should be completed prior to discharge to evaluate if the permeate requires further treatment.

Sulfite allergies are relatively common; 1.1–4.5% of the general population are sensitive to sulfites and about 39.9% of positive test results are considered clinically relevant (Madan *et al.* 2007; García-Gavín *et al.* 2012; Häberle *et al.* 2016). The risk of severe reactions in certain individuals necessitates careful handling of SBS, especially since occupational exposure is one of the most common sources responsible for the presentation of sulfite sensitivities (Madan *et al.* 2007; Vally & Misso 2012). If there are significant levels of SBS in distributed waters, its oxygen scavenging potential has been shown to threaten certain aquatic environments; however, SBS does not pose a significant risk to the overall environment as it quickly biodegrades (EFSA ANS Panel 2016).

Advantages and limitations

By reducing oxygen concentrations, SBS controls aerobic bacterial growth and effectively reduces the potential for membrane fouling. However, the efficacy of shock dosing SBS has been debated for marine bacteria and microflora, and shock dosing has been proven ineffective against microorganisms that can adapt to anaerobic conditions (Baker & Dudley 1998). Additionally, the application of SBS is limited to relatively clean water, as it is ineffective against existing biofilms and high-fouling potential water (Redondo & Lomax 2001). SBS dosing is also not recommended in cases where the feed water contains heavy metals, as they react with SBS residual, forming oxidants and fouling the membrane (Dow 2011). The optimum dosing concentration of SBS is dependent on the type of microorganism present and varies as the composition of the feed water changes, making the optimal dosing concentration of the biocide difficult to maintain. Further, SBS is more effective at a lower pH, which is not compatible with RO system components. Methods for monitoring SBS dosage, other than monitoring the pH of the feed water and biocide solution, were not found in the literature. Overdosing SBS will potentially cause a higher residual concentration in the permeate stream, decreasing pH and dissolved oxygen content thus posing a threat to aquatic life, or killing gastrointestinal bacteria after human consumption (Ryon *et al.* 2002; Irwin *et al.* 2017). As a result, treatment with SBS requires off-line dosing in potable water applications and careful monitoring of permeate and concentrate quality when distributing water to sensitive aquatic environments. A study by Majamaa *et al.* (2011), on the comparison of non-oxidizing biocides with SMBS, concluded that SBS is a relatively costly method for limiting biofouling in storage, due to the high concentration of chemical required and short preservation time in comparison to other non-oxidizing biocides.

Although comparatively costly, SBS in solution is easy to use as it can be directly injected into the feed stream during normal plant operation and can be easily stored as SMBS (Dow 2011). Additionally, SBS is formed by dissolving SMBS in water, indicating very easy generation (Dow 2011). Other advantages include that, along with limiting microbial fouling in RO systems, SBS dosing can be used to control colloidal fouling (Redondo & Lomax 2001; Singh 2015) and the acidic reaction of SBS allows for calcium carbonate control (Wei *et al.* 2012). Overall, the compatibility of SBS with polyamide membranes, its widespread use as a preservative during membrane storage, and its easy application make it a worthy prospect to investigate further as a preventative biocide in RO systems.

PHENOXYETHANOL (PE)

2-phenoxyethanol (PE), an aromatic glycol ether, is widely used as a personal care product preservative due to its broad antimicrobial activity (Paulus 2005; Puschmann *et al.* 2018; Akgündüz *et al.* 2020). PE is commonly added to cosmetic and

pharmaceutical products, such as hand disinfecting biocidal products and vaccines (ECHA 2018; Puschmann *et al.* 2018). PE is a biocide of special interest, due to its chemical and physical properties, including effectiveness as a solvent and antimicrobial (Paulus 2005; Lilienblum 2016). The preservative, naturally found in green tea, has a weaker inhibitory effect on desirable skin-resident bacteria than other cosmetic chemicals preservatives (Lilienblum 2016); therefore, PE is used in a large range of skincare and cosmetic products, such as mascara and sunscreen creams (Hawley 1971; Gosselin *et al.* 1976; Kabara 1984). Although there is no evidence of PE application to industrial water systems in literature studies, PE exhibits beneficial characteristics as a biocide and may have the potential for use on RO systems (Curtin 2020; Curtin *et al.* 2021).

Generation

2-phenoxyethanol is manufactured by processing phenol with ethylene oxide in the presence of a catalyst under pressure and high temperatures (Kabara 1984). The preservative is commonly produced in laboratories due to the importance of purity in the cosmetic and pharmaceutical industry (Akgündüz *et al.* 2020). Stability of the biocide has been demonstrated and preservative activity does not decrease with time; PE can withstand prolonged storage, transportation, or use (Paulus 2005).

Mechanisms of action

2-phenoxyethanol has a large spectrum of antimicrobial activity and is effective against Gram-negative, Gram-positive, molds, and yeast (Dréno *et al.* 2019; Canavez *et al.* 2021). It is noted that PE is more effective against Gram-positive than Gram-negative bacteria (Paulus 2005). The mechanism of action of PE is as a lytic membrane-active biocide (Chapman 2003). It acts by disrupting the bacterial cell membrane, leading to rapid cell lysis and leakage of the cellular protein (Gilbert *et al.* 1977; Fitzgerald *et al.* 1992). PE destabilizes the cell membrane by uncoupling oxidative phosphorylation, preventing respiration, and obstructing malate dehydrogenase (Dréno *et al.* 2019), an enzyme responsible for a metabolic reaction pathway (Cunningham *et al.* 1997). PE also acts as a biocide by using a direct inhibitory effect on microbial DNA and RNA synthesis and increases the permeability of the cell membrane to potassium ions (CIR 1990), resulting in cell death.

Anti-biofouling effect: dosage and efficacy

In the health and personal care industries, PE is used as a preservative or antimicrobial agent with the typical concentration range from 5,000 to 10,000 mg/L (Paulus 2005). The biocidal efficacy of PE is most effective in the pH range of 4–5 (Paulus 2005). According to Paulus (2005), the use of PE alone in formulations is rarely sufficient in terms of efficacy. To increase the antimicrobial efficacy, PE is generally blended with other preservatives such as dibromodicyanobutane, PHB ester, iodopropylbutylcarbamate, and formaldehyde.

The efficacy of PE, including the MIC, MBIC, and MBEC are displayed in Table 2. The inhibitory concentrations presented in Table 2 indicate that PE will be more effective at lower concentrations to prevent biofouling compared to removing the existing biofilm as indicated by the MBIC and MBEC, respectively. The information also confirms that PE is a weaker antimicrobial when compared to DBNPA or MIT and will need to be applied to RO at higher concentrations (Kim & Park 2015; Curtin 2020; Curtin *et al.* 2021).

Membrane compatibility

There were no studies in the literature of PE being used as a biocide to prevent biofouling in water treatment applications, including RO, or for membrane storage, therefore, no studies verifying PE compatibility with RO membranes. However, due to its non-oxidizing nature, we hypothesize that PE is compatible with polyamide membranes.

Human and environmental health hazards

The use of PE is considered safe for consumers of all ages when applied as a preservative in cosmetic products at a maximum concentration of 10,000 mg/L (DEPA 2015; Lilienblum 2016). PE is a rare sensitizer and is considered one of the most well-tolerated preservatives used in personal care products (NASMHP 2019). PE can cause toxic effects if inhaled, ingested, or skin contact, including skin, lung and liver irritation, kidney, and liver damage (Dréno *et al.* 2019; Akgündüz *et al.* 2020). Moreover, the U.S. Food and Drug Administration reported that high doses of PE may cause dehydration, vomiting, nervous system problems, and diarrhea in infants and nursing mothers (Hall & Al 1981; Mácová *et al.* 2008). Therefore, safety precautions and appropriate personal protective equipment must be considered when handling PE concentrations over 10,000 mg/L.

In several studies, PE is confirmed as a very low hazard for environmental fate, including persistence and bioaccumulation (ECHA 2015; CPA 2016). Researchers Lyman *et al.* (1990) estimate that PE will not hydrolyze in the environment because of the absence of functional groups that hydrolyze under environmental conditions (Supplementary Material, Tables S1 and S2). In addition, acute aquatic toxicity and chronic aquatic toxicity scored low hazard based on the LC/EC₅₀ and NOEC values (ECHA 2015). However, the chronic aquatic NOEC values are assigned low confidence and therefore additional testing is required. In summary, PE generally has minimal impact on the environment and aquatic life and is therefore inherently safer for water treatment applications than many other choices.

Advantages and limitations

A major limitation of PE involves the low biocidal efficacy, indicated by the high MIC and MBEC values which would result in higher concentrations needed when applied to RO systems (Curtin 2020; Curtin *et al.* 2021). The larger dosage will result in the application of PE to be more expensive, even though the preservative is known to be low cost in the cosmetic industry (Weyl *et al.* 1996). As a result of the high concentration required for application, the presence of total dissolved solids will increase, potentially exceeding water quality guidelines. Another drawback of PE is there is no evidence that PE is compatible with polyamide membranes, disinfects the permeate, or whether it is more effective at preventing or removing biofouling when dosed continuously or intermittently. Nevertheless, since PE is a non-oxidizing biocide, it can be hypothesized that PE will be compatible with polyamide membranes. The advantages of 2-phenoxyethanol include the preservative stability and solubility (Poudrier 1990; Paulus 2005). PE is soluble in water at 26,700 mg/L water at 20 °C (Haynes 2010). The preservative stability benefits the application for water treatment, including ease of chemical injection, storage, and versatile use including membrane storage. Other advantages of PE include low environmental and human impact, so handling and disposing of biocide waste will likely be safe when concentrations are less than 10,000 mg/L (DEPA 2015; ECHA 2015; Lilienblum 2016).

SODIUM BENZOATE

Sodium benzoate is the sodium salt of benzoic acid. Benzoic acid is the simplest aromatic carboxylic acid and it is commonly found in nature (Qualley *et al.* 2012). Chipley *et al.* (2020) reported that SB is inexpensive and easy to obtain. It is used as a preservative in cosmetic and personal care products, such as foundation, cologne, shampoo, and moisturizer. (CIR 2001). It is used as an antimicrobial in food and is Generally Recognized as Safe (GRAS) by the United States Food and Drug Administration up to a concentration of 1,000 mg/L (CFR 2020). Many bacterial and fungal species are effectively inhibited and killed by SB (Karabay *et al.* 2006). SB is used in pharmacology to treat urea cycle disorders (Husson *et al.* 2016), acute hepatic encephalopathy (Sushma *et al.* 1992), as an add-on drug to treat schizophrenia (Lane *et al.* 2013), and in combination with other compounds to treat various types of headaches (Yucel *et al.* 1999). SB is not used in polyamide membrane systems but it is a promising antimicrobial because it is inexpensive, very soluble in water, and kills a variety of microorganisms.

Generation

The synthesis of SB consists of the neutralization of benzoic acid using sodium bicarbonate, sodium carbonate, or sodium hydroxide (WHO 2000; Johnson *et al.* 2017) as shown in Figure 4. Benzoic acid is produced by the decarboxylation of phthalic anhydride, alternatively, the chlorination of toluene to benzotrichloride, which is hydrolyzed to benzoic acid (Johnson *et al.* 2017). Benzoic acid can also be produced via the liquid phase oxidation of toluene (WHO 2000).

Mechanisms of action

Sodium benzoate is a weak acid with a pKa of 4.2 (Sagoo *et al.* 2002). Weak acid preservatives are more generally effective at lower pH values because a larger portion of the acid molecules is neutrally charged. If a molecule is neutrally charged, there is

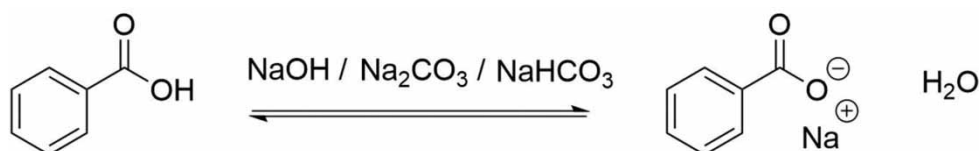


Figure 4 | Neutralization of benzoic acid.

a higher chance of it diffusing across a cell membrane. Krebs *et al.* (1983) showed that benzoate acts as an antifungal against *S. cerevisiae* by greatly decreasing the intracellular pH. At low extracellular pH, neutral benzoic acid diffuses into the intracellular space at which point the benzoic acid is subjected to physiological pH 7.4. Since the intracellular pH is higher than the pKa of benzoic acid, it dissociates from its acidic proton. The yeast was able to maintain a physiological pH in media conditions that ranged from pH 2.5 to 7.4 in the absence of SB. The researchers noticed there was a great decrease in intracellular adenosine triphosphate (ATP) upon treatment with benzoate. Krebs *et al.* (1983) hypothesized that benzoate inhibited glycolytic enzymes such as phosphofructokinase but this hypothesis was rejected when there was no specific blockage of glycolysis (Warth 1991). Between 60 and 120 mg/L of benzoic acid, Warth (1991) found the fermentation rate, ATP concentration, and intracellular pH of *S. cerevisiae* declined. At relatively high benzoic acid concentrations, 0.12–300 mg/L, growth was fully inhibited but the cells did not rapidly die. A similar mechanism is believed to be the reason for the antibacterial effects of SB. When the intracellular pH decreases, the bacterium must pump protons out of the cell to maintain physiological pH (Chen & Zhong 2018). This pumping consumes ATP which inhibits bacterial growth and can result in cell death. Based on this mechanism, it is classified as a protonophore (Figure 3). The antimicrobial activity of benzoate is effective against fungi, Gram-positive bacteria, and Gram-negative bacteria.

Anti-biofouling effect: dosage and efficacy

Table 2 shows the inhibitory concentrations of SB against relevant biofilm pioneer microorganisms. Karabay & Sahin (2005) reported that SB was effective against methicillin-resistant *S. aureus* (MRSA), and methicillin-sensitive *S. aureus* (MSSA) isolates *in vitro*. MSSA and MRSA isolates were obtained from hospitalized patients. Both isolates were sensitive at SB concentrations of 32 mg/L and up. Karabay *et al.* (2006) also studied the activity of SB against *Enterococcus* species. The authors found that the minimum concentration of SB used to inhibit 90% of microorganism growth (MIC₉₀) against *E. faecalis* was 64 and 32 mg/L against *E. faecium*. *Salmonella* species were isolated and cultured from chicken samples by Er *et al.* (2014), and the antibacterial properties of preservatives were tested in microtiter plates. The MIC of SB was found to range from 25 to 250 mg/L at pH 7, whereas the MBEC was 1,600–7,600 mg/L. Bacteria were consistently inhibited more effectively at lower pH. There have been no experiments using SB to prevent or treat biofouling in RO systems.

Haque *et al.* (2005) assessed preventing bacterial attachment and biofilm formation in fresh water using SB. The authors used SB dispersed in solution and entrapped in silicone coatings over a sampling period of 28 days. The optimal concentration of dispersed SB was 700 mg/L. This concentration led to 3.3% biofilm surface coverage (79% reduction relative to control) of silicone slides after 28 days. The bacteria were isolated from fresh lake water and enriched during the challenge period of SB incubation.

Membrane compatibility

The direct application of SB in RO systems has not been demonstrated yet. Mohammad & Ali (2002) used SB along with other chemicals of interest to study rejection rates of polyamide nanofiltration (NF) membranes. The researchers concluded that SB was consistently rejected by NF membranes and it did not reduce the salt rejection of the membranes over time for different permeate fluxes signifying no inherent membrane degradation. The results support the potential polyamide NF membrane compatibility with SB; however, no direct analysis of degradation on the polyamide surface was completed. The results reported by Mohammad & Ali (2002) indicate that SB might also be directly compatible with polyamide RO membranes since NF membranes and RO membranes are made of the same polymeric materials. This is supported by the mechanism of antimicrobial action of SB, which is non-oxidizing.

Human and environmental health hazards

The biodegradation of SB is rapid in aerobic, aqueous conditions such as seawater (WHO 2000). No experimental data is available detailing the accumulation of SB in the environment, but it acts similarly to benzoic acid, which poses a low environmental hazard (Supplementary Material, Tables S1 and S2). In the mitochondria, SB and glycine are combined to form hippurate, which is then cleared by the kidneys (Badenhorst *et al.* 2014). SB is metabolized into hippurate to increase hydrophilicity, which decreases the diffusion of benzoate back over the inner mitochondrial matrix. Lennerz *et al.* (2015) performed oral administration of the GRAS dose of SB in combination with glucose to study its effect on glucose homeostasis in humans. They found no statistically significant difference in serum insulin or plasma glucose between consumption of glucose beverages with and without SB. Ingestion of SB was found to significantly influence circulating hippurate, acetyl lysine, and anthranilic acid. Benzoate caused a significant decrease in glycine. Lennerz *et al.* (2015) provided good insight into the

acute effects of GRAS benzoate consumption, but the study does not allow us to draw conclusions about long-term exposures or doses higher than the GRAS dose. Considering this evidence, SB has low human and environmental risk generally, and especially when compared to other biocides used in water treatment.

Advantages and limitations

Sodium benzoate is very soluble in water, up to 550,000 mg/L (Haque *et al.* 2005), which enables practical use in RO systems. SB is relatively inexpensive compared to other non-oxidizing biocides such as MIT and DBNPA. It is similarly priced to PE and SBS from common chemical suppliers. Depending on the microorganism PE may be more or less effective per dollar spent than SB (Table 2). SBS is less expensive than SB to achieve similar outcomes. The human and environmental hazards are low and SB is biodegradable. SB has relatively high MIC, MBIC, and MBEC values, which would require larger doses when compared to other antimicrobials to achieve similar outcomes (Table 2). This drawback can be offset by how inexpensive it is. According to Mohammad & Ali (2002), SB does not pass into the permeate, and therefore, does not disinfect it. To date, SB has not been used in RO application but it is a promising biocide that poses a little relative hazard to humans and the environment (Tables 3 and 4).

OTHER NON-OXIDIZING BIOCIDES

We have selected an additional four non-oxidizing biocides that are promising for use in RO applications. These biocides have not necessarily been studied in membrane applications, but based on their antimicrobial properties and compatibility, we believe they should be considered for future research and use. Limited data have been reported on these chemicals and whether they can effectively prevent biofouling. Human and environmental toxicity studies should be done on these additional biocides to determine if they are suitable for potable water uses.

Lauroyl arginate ethyl

Lauroyl arginate ethyl (LAE) is a cationic biocide that acts by interacting with the negatively charged membrane of bacteria, which ruins its integrity (Kim & Park 2016). LAE was approved as a food additive by the FDA in 2005 (U.S. FDA 2005). It is currently used as a preservative for food and beverages (Woodcock *et al.* 2009) and is found in some mouthwashes (Pilloni *et al.* 2018). Kim & Park (2016) evaluated LAE for use in RO systems and found that it does not damage polyamide membranes. Four bacterial species of interest (*P. aeruginosa*, *E. coli*, *S. aureus*, and *E. faecalis*) were used to test LAE and DBNPA to compare antimicrobial activities. LAE had a higher killing effect than DBNPA against every bacteria tested in suspension. LAE was also superior to DBNPA at inhibiting biofilm formation and destroying biofilms. The water flux of a polyamide membrane was not influenced by increasing concentrations of LAE except for at 100,000 mg/L which the authors proposed was caused by residual LAE on the membrane surface. Hawkins *et al.* (2009) studied the *in vitro* and *in vivo* metabolism of LAE in humans. The authors found LAE was rapidly metabolized into naturally occurring dietary molecules and concluded it poses little to no safety risk as a food preservative. One drawback of LAE is how expensive it is (Kim & Park 2016). Overall, because of its low toxicity, antimicrobial properties, and membrane compatibility, LAE is a very promising chemical for polyamide filtration use.

Polyhexamethylene guanidine hydrochloride

Polyhexamethylene guanidine hydrochloride (PHMGH) is a cationic polymer that has shown to be strongly biocidal yet has low toxicity to humans (Park *et al.* 2020). PHMG is written as an ambiguous salt form of PHMG, whereas PHMGH specifies the hydrochloride salt. Oulé *et al.* (2008) showed that PHMGH acts as an antimicrobial by causing tears in the cell membrane, which spills the cytoplasmic contents into the media and kills the cell. The positive charge of PHMGH interacts strongly with bacterial membranes and displaces stabilizing Mg^{2+} and Ca^{2+} . Suspensions of *S. aureus* and *P. aeruginosa* were treated with various molecular structures of PHMG by Wei *et al.* (2009), and it was found that aqueous PHMGH had excellent antimicrobial activity when the molecular weight was above 640 Da. Kim *et al.* (2016) subjected rats to aerosolized 100 nm PHMG-phosphate particles to study pulmonary inflammatory and fibrotic responses. The researchers found inflammatory cytokines, ROS generation, fibrosis, and airway barrier injuries in the rats. Mathurin *et al.* (2012) tested PHMGH against several reference bacteria and fungi. The researchers proposed that PHMGH was less effective against fungi compared to bacteria because of their rigid cell wall. PHMG was reacted with ethylene glycol diglycidyl ether and subsequently chemically grafted onto polyamide (PA6) membranes (Ye *et al.* 2020) to study its antimicrobial and chemical properties. The PHMG bonded to the polyamide membranes inhibited the growth of *E. coli* and *S. aureus* by more than

99.99%. Additionally, the study showed that PHMG did become unbonded from the membrane and leach into the water, and the modified membranes kept their mechanical properties. It has been used in cooling water systems (Amjad & Demadis 2015) but not in RO systems.

Benzyldimethyldodecyl ammonium chloride

Benzyldimethyldodecyl ammonium chloride (BDMDAC) is a quaternary ammonium salt agent and cationic biocide, routinely used as a disinfectant in swimming pools and industrial cooling water systems (Ferreira *et al.* 2009; Liu *et al.* 2011). BDMDAC forms an electrostatic bond with the negatively charged sites on microbial cell walls, causing cell lysis, disruption of cell-wall permeability, and reduced intake of nutrients to the cell (Liu *et al.* 2011). BDMDAC has very good inactivation potential, but Gomes *et al.* (2014) concluded that it was unsuccessful at removing biofilms. Further, BDMDAC has been found to be notoriously ineffective for Gram-negative bacteria, specifically, *P. aeruginosa* (Hegstad *et al.* 2010). Alternatively, Gomes *et al.* (2021) found that BDMDAC in combination with mechanical stress was effective in removing mature biofilms, although not completely. A study by Hegstad *et al.* (2010) reported that quaternary ammonium compounds (QACs) generally have poor degradability and that the concentration of QACs in sewage depends on the alkyl chain length, of which C12 (the alkyl chain length of BDMDAC) was the most prevalent. Additionally, QACs are generally low cost but can be deactivated by hardness and have poor compatibility with polyanionic polymers (Frayne 2001). The ineffectiveness of BDMDAC on the primary microbiological problem area, Gram-negative bacteria, along with the observed retention in sewers and receiving waters, limits the application of BDMDAC and other QACs as biocides in RO systems. As a result, BDMDAC is not considered a promising candidate for application as a preventative biocide in RO systems.

Sodium nitroprusside

Sodium nitroprusside (SNP), a nitric oxide (NO) donor compound, has a direct effect on biofilm reduction through the release of the NO free radical. SNP releases NO at picomolar and nanomolar levels, which have been shown to interact with sessile *P. aeruginosa* cells and function as a signal for the cells to transition back into a planktonic-like state, resulting in the reduction of total biofilm surface and the restoration of cell vulnerability to antimicrobials (Barraud *et al.* 2009; Nguyen *et al.* 2012). Alternatively, Nagaraja *et al.* (2017) concluded that SNP acts by degrading polysaccharides in the biofilm layer. SNP is highly soluble in water (400 g/L, 25 °C) and has the greatest efficacy at pH 5.0, with decreasing amounts of NO released up to pH 7.2 (Nagaraja *et al.* 2017). Multiple studies have found NO donor compounds to be effective against both Gram-positive and Gram-negative bacteria, and overall broadly effective on single- and multi-species biofilms (Hetrick *et al.* 2008; Barraud *et al.* 2009). This is supported by Nagaraja *et al.* (2017), who reported that SNP effectively dispersed a multi-species biofilm from an industrially fouled RO membrane. Further, SNP was found to be more effective in recovering membrane permeability as compared to DBNPA (Nagaraja *et al.* 2017). The concentration of released NO that is effective against biofilms is several orders of magnitude below toxic levels and so should not pose a threat to humans or the environment (Barraud *et al.* 2009; Nagaraja *et al.* 2017). Although results from previous studies look promising, a recent paper reports that some bacterial pathogens have evolved mechanisms for NO resistance (Hoeck 2017). Still, NO donor compounds such as SNP, which are still in the pilot-scale of testing, can be further investigated for compatibility with RO membranes and efficacy in RO systems.

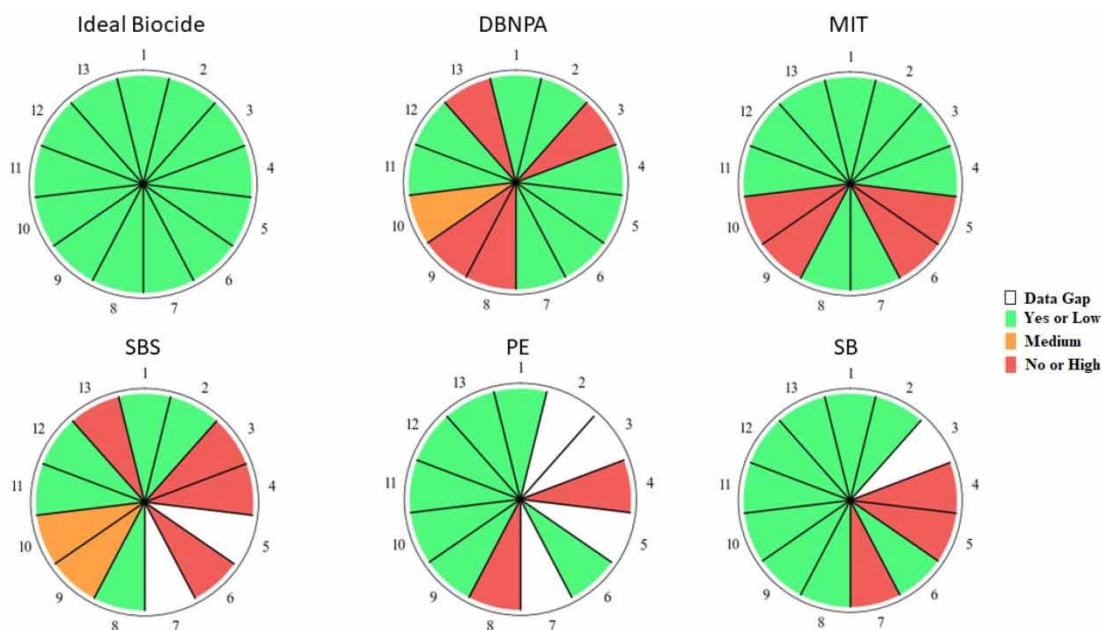
DISCUSSION

The biofouling of polyamide membranes is one of the most challenging barriers faced by RO technologies to achieve a sustainable water supply. Membrane biofouling results in (1) an increase in the energy demand and capital cost of RO systems, (2) reduction of membrane lifespan due to frequent cleanings, and (3) loss of productivity. According to Kucera (2019), the traditional methods applied to address biofouling, feed pretreatment by chlorine disinfection, and membrane cleaning by non-oxidizing biocides, are not efficient to solve the problem of biofouling because they are not preventive techniques. To overcome these issues, the introduction of new sustainable anti-biofouling agents and practices to the RO market is necessary. Based on the work presented herein, there are many potential candidates to prevent biofouling in RO systems. These biocides may come either from the non-oxidizing biocides already applied in RO installations, such as MIT, DBNPA, and SBS or low-hazard chemicals like SB and PE. However, the main limitation to finding an ideal biocide to address polyamide membrane

biofouling relies on the difficulty to find antifoulants that are (a) efficient in preventing and treating biofilms, (b) compatible with membranes, (c) non-hazardous, and (d) inexpensive.

Figure 5 provides a comparison between an ideal biocide applicable to biofouling prevention and control in polyamide membrane systems and the five selected biocides discussed herein. Table 5 presents a summary of the main advantages and limitations of all anti-biofouling agents reviewed in this study in addressing biofouling prevention in RO systems. Among all five biocides discussed in detail, in terms of inhibitory concentrations (Table 2) and effectiveness against a wide spectrum of microorganisms (Figure 5), MIT presented the best antimicrobial efficiencies to prevent and disinfect membrane biofouling. On the other hand, due to the high doses needed for biofouling control and toxicity, MIT also presented the highest hazards to humans and aquatic life if compared to the other biocides, limiting its use in continuous inline water applications. DBNPA showed to be effective against biofouling prevention in clean membranes, showing a fast kill response and good compatibility with polyamide membranes. The studies discussed in this paper indicated that DBNPA is not effective against existing biofilms. It also has a short half-life of around 24 h in pH levels typical of polyamide membrane applications, and it may present adverse effects to humans and the environment (Figure 5 and Table 5). These constraints limit the long-term application of DBNPA in biofouling prevention in drinking water applications.

Different from the other two commercial non-oxidizing biocides applied in the RO market (DBNPA and MIT), SBS can be applied in continuous inline drinking water applications. Nevertheless, high concentrations of SBS in the water distribution system due to overfeeding may pose adverse effects to humans if ingested, and to aquatic life. In polyamide membrane applications, SBS is the standard chemical for dechlorination and membrane storage (Kucera 2019). According to the literature, SBS presented moderate antimicrobial effects against aerobic bacteria, as compared to other chemicals; however, it was not effective against anaerobic bacteria or existing biofilms (Figure 5, Tables 2 and 5). SBS is also more effective at low pH, which is a concern for RO applications because low pH levels damage polyamide membranes. The high doses and associated costs required to prevent microbial growth, along with the efficacy of the biocide restricted to low-fouling potential water, limit the application of SBS for biofouling prevention in RO systems. Further research needs to be done to determine minimum inhibitory concentrations of biofilm pioneers in RO systems for SBS as well as DBNPA (Table 2). For these reasons, the application of DBNPA, MIT, or SBS is not recommended as a permanent solution to prevent biofouling in potable water membrane system applications.



1 – Biodegradable; 2 – Membrane compatible; 3 – Break up biofilms; 4 – Inexpensive; 5 – Disinfects permeate; 6 – Easily disposed; 7 – Easily monitored; 8 – Easily injected; 9 – Environmental hazard; 10 – Human hazard; 11 – Bactericide; 12 – Fungicide; 13 – Algaecide.

Figure 5 | Ideal biocide for RO polyamide membrane applications. White color refers to data gaps. Green refers to 'yes' or low-hazard level, orange refers to medium hazard level, and Red refers to 'no' or high hazard level. Please refer to the online version of this paper to see this figure in colour: <http://dx.doi.org/10.2166/aqua.2022.118>.

Table 5 | Summary of main advantages and limitations of non-oxidizing biocides for biofouling prevention in polyamide membrane systems

Biocide	Advantages	Limitations	Development stage
DBNPA	1 – Fast biocidal activity ^a 2 – Prevents biofilms well ^c	1 – Not effective against existing biofilms ^b 2 – Short half-life at pH higher than 7 ^d	Full-scale applications
MIT	1 – Effective against a wide range of microorganisms ^e 2 – Inhibits growth and kills biofilm pioneers ^c	1 – Hazardous chemical ^e 2 – RO concentrate needs to be treated ^f	Full-scale applications
SBS	1 – Good for long-term RO applications ^c 2 – Effective against biofilm pioneers ^c	1 – Not effective against anaerobic bacteria ^c 2 – Expensive compared to other biocides ^g	Full-scale applications
PE	1 – Effective against biofilm pioneers ^h 2 – Low hazards ^h	1 – High doses needed for biofouling prevention ^h	Under development stage
SB	1 – Effective against biofilm pioneers ^h 2 – Inexpensive ⁱ	1 – Moderate doses needed for biofouling prevention ^h	Under development stage
LAE	1 – Compatible with polyamide membranes ^j 2 – Treats and prevents biofilms ^j	1 – More effective against bacteria in suspension ^j	Under development stage
PHMGH	1 – Effective against biofilm pioneers ^k 2 – Low hazards ^l	1 – Less effective against fungi ^m	Under development stage
BDMDAC	1 – Low hazards ⁿ	1 – Not effective in removing existing biofilms ^o 2 – Not effective against biofilm pioneers ^p	Under development stage
SNP	1 – Effective against biofilm pioneers ^q 2 – Removes existing biofilm ^q	1 – Hazardous at high concentrations ^r 2 – May lead to microbial resistance ^s	Under development stage

Source: ^aSchook *et al.* (2012), ^bSiddiqui *et al.* (2017), ^cKucera (2019), ^dExner *et al.* (1973), ^eSilva *et al.* (2020), ^fLi *et al.* (2016), ^gMajamaa *et al.* (2011), ^hCurtin (2020), ⁱChipley *et al.* (2020), ^jKim & Park (2016), ^kWei *et al.* (2009), ^lPark *et al.* (2020), ^mMathurin *et al.* (2012), ⁿTan *et al.* (2017), ^oGomes *et al.* (2014), ^pHegstad *et al.* (2010), ^qBarraud *et al.* (2009), ^rNguyen *et al.* (2012) and ^sHoeck (2017).

Despite the factors limiting the application of these three commercial biocides, they should still be considered in RO biofouling control and prevention studies. This is because each of these three imperfect biocides is a model of several of the features found in the ideal biocide described by Bates (1998). MIT is a good model of a biocide that presents high antimicrobial efficiency as it is concurrently effective in preventing and removing existing biofilms. DBNPA is a good reference for a fast response biocide which is effective in biofilm prevention. SBS is a model for a low-hazard chemical that is compatible with polyamide membranes and effective against biofilm pioneers. It is important to notice that the discussion of biofouling prevention should also include biofouling treatment. As such, the search for low-hazard alternatives, simultaneously effective in biofouling prevention and biofilm removal, should be continued.

According to the results summarized in Figure 5, PE and SB presented lower human and environmental hazards as compared to MIT and DBNPA. PE was the safest chemical among all five biocides and both PE and SB are able to prevent biofilm pioneers (Figure 5 and Table 5). However, although PE and SB are not expensive products, the relatively high doses required to achieve biofouling prevention would make their application quite expensive and allowable concentrations a significant concern, limiting the use of these biocides in potable water RO applications (Figure 5 and Table 5). Furthermore, similar to SBS, PE and SB biocides are most effective at low pH, which makes their use for continuous treatment in polyamide membranes less attractive. Therefore, further studies need to be conducted to evaluate the feasibility of applying SB and PE in biofouling prevention in polyamide membrane systems.

Several promising non-oxidizing biocides in the very early stages of development were identified in this paper (Table 5). Among the promising non-oxidizing biocides discussed herein, LAE and PHMGH showed to be the most attractive candidates to prevent biofouling in RO systems due to their high effectiveness against biofilm pioneers and low associated hazards. However, comprehensive studies on membrane compatibility, human and environmental hazards, biocidal effectiveness against dynamic biofilms, and RO market readiness are necessary to determine the feasibility and applicability of those chemicals in potable water RO system applications.

In this review, many research gaps were identified in the process of selecting an effective, economic, and eco-friendly biocide applicable to polyamide membrane systems. Biofouling prevention studies are almost non-existent in the literature and unlike for the prevention of planktonic microbial growth (CLSI-M02 2018; CLSI-M07 2018; CLSI-M11 2018; CLSI-M100 2021), there

are no standard protocols available to test new biocides for biofouling prevention in RO systems. Although there is still a need for standardized protocols to test the efficacy of biocides in preventing biofouling, the metrics and figures of merit for comprehensive monitoring and diagnosis of membrane biofouling are well known (Kucera 2015). A sizable body of literature exists already on different methodologies to perform (a) membrane autopsies, (b) biofilm detection, (c) impacts of biofouling on RO systems' performance, (d) risk assessment, and (e) antimicrobial efficacy analysis (Nguyen *et al.* 2012; Kucera 2015; Curtin 2020; Curtin *et al.* 2021). The translation of research study standard protocols to the industry will depend on the metrics selected to measure biofouling. There are various techniques available to investigate the effects of biofouling on membrane systems in an academic laboratory with spectroscopic facilities, while the majority of available research techniques may be limited in industry. Therefore, the industry applicability of standard protocols and techniques is necessary for testing the effectiveness of biocides in RO systems. Furthermore, more studies need to be done to investigate the long-term application of the selected biocides as well as new alternatives for preventing biofouling in RO systems. With the exception of DBNPA, no studies from laboratory-scale to full-scale in RO treatment units were found in the literature investigating the use of MIT, PE, SB, and SBS to prevent biofouling in RO systems. Also, further research needs to be performed to evaluate the polyamide membrane compatibility of PE and SB. Moreover, more studies need to be conducted to determine minimum inhibitory concentrations against known biofilm pioneers (including *P. aeruginosa* and *S. aureus*) for all biocides, specifically for DBNPA and SBS.

CONCLUSIONS AND PROSPECTS

The biofouling of polyamide membranes results in detrimental effects on the performance of RO systems such as an increase in the required operational pressure, a decrease of freshwater production, shortening of membrane lifetime, and increase of operational cost and energy consumption. Overcoming the existing challenges of biofouling in membrane systems is essential to promote sustainable water supply in water-stressed countries. To overcome these challenges, the introduction of new sustainable anti-biofouling agents into the RO market is necessary. This review provided a comprehensive analysis of the applicability of five non-oxidizing biocides (MIT, DBNPA, SBS, PE, and SB) to prevent biofouling in polyamide membranes to optimize RO system performance in drinking water applications. To summarize the major results for each biocide in addressing biofouling in RO systems: (1) MIT presented better antimicrobial efficiencies to prevent and disinfect biofilms in polyamide membranes when compared to other biocides; however, its use in potable water applications may pose threat to humans and the environment; (2) DBNPA showed to be very efficient in preventing biofouling, but its short half-life around neutral pH, low efficiencies against mature biofilm, and hazards limit its application in drinking water treatment by RO technologies; (3) SBS may be applicable inline RO application for potable water treatment. However, its low antimicrobial efficiency and pH effectiveness dependency bring concerns for RO applications; and (4) PE and SB were the safest biocides; however, the high doses required to prevent biofouling may limit their application in polyamide membrane separation technologies. Overall, MIT and DBNPA are excellent models for biofouling prevention studies, between them possessing most of the key features of an ideal biocide when compared to the other biocides discussed in this study. SBS provides a great reference for antimicrobial efficiency against biofilm pioneers. PE and SB provide a good model for low-hazard biocides.

Based on this review, further research efforts should focus on (a) identifying inhibitory concentrations of these biocides against biofilm pioneers such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*; (b) testing the applicability of these chemistries in preventing and controlling biofouling of polyamide membranes through long-term biofouling prevention studies on laboratory-scale, pilot, and full-scale RO treatment systems; (c) verifying the compatibility with polyamide membranes through short and long-term exposure studies, and (d) developing protocols to test the efficacy of green biocides preventing biofouling in RO systems; (e) finding better candidates for biofouling prevention. Ultimately, these studies will result in the optimization of RO system performance, minimization of operational costs and energy consumption, increase in reliability and environmental performance, and ensure the sustainable application of RO technologies in mitigating water scarcity.

ACKNOWLEDGEMENTS

This work was accomplished at the Civil Engineering Department, Green Safe Water Lab, University of Victoria, Victoria, British Columbia, Canada.

AUTHOR CONTRIBUTIONS

Luiz H. Da-Silva-Correa, Hayley Smith, Matthew C. Thibodeau, and Bethany Welsh performed this critical review with the guidance of H.L. Buckley. Luiz H. Da-Silva-Correa wrote the discussion of the information derived from the analyzed literature with assistance from Hayley Smith, Matthew C. Thibodeau, and Bethany Welsh. Luiz H. Da-Silva-Correa led manuscript preparation. H. L. Buckley provided feedback and revised the manuscript. H. L. Buckley secured funding for this project.

FUNDING

This research was funded by Electricity HR, NSERC USRA, NSERC Discovery, CEWIL, and University of Victoria.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

REFERENCES

- Abd El Aleem, F. A., Al-Sugair, K. A. & Alahmad, M. I. 1998 Biofouling problems in membrane processes for water desalination and reuse in Saudi Arabia. *International Biodeterioration & Biodegradation* **41** (1), 19–23. [https://doi.org/10.1016/S0964-8305\(98\)80004-8](https://doi.org/10.1016/S0964-8305(98)80004-8).
- Achinas, S., Charalampogiannis, N. & Euverink, G. J. W. 2019 A brief recap of microbial adhesion and biofilms. *Applied Sciences* **9** (14), 2801. <https://doi.org/10.3390/app9142801>.
- Aerts, O., Goossens, A., Lambert, J. & Lepoittevin, J. P. 2017 Contact allergy caused by isothiazolinone derivatives: an overview of non-cosmetic and unusual cosmetic sources. *European Journal of Dermatology* **27** (2), 115–122. <https://doi.org/10.1684/ejd.2016.2951>.
- Akgündüz, M. Ç., Çavuşoğlu, K. & Yalçın, E. 2020 The potential risk assessment of phenoxyethanol with a versatile model system. *Scientific Reports* **10** (1), 1–10. <https://doi.org/10.1038/s41598-020-58170-9>.
- Al-Ahmad, M., Aleem, F. A., Mutiri, A. & Ubaisy, A. 2000 Biofouling in RO membrane systems Part 1: fundamentals and control. *Desalination* **132** (1–3), 173–179. [https://doi.org/10.1016/S0011-9164\(00\)00146-6](https://doi.org/10.1016/S0011-9164(00)00146-6).
- Alexander, W. K., Briggs, G. B., Still, K. R., Jederberg, W. W., MacMahon, K., Baker, W. H. & Mackerer, C. 2001 Toxicity of 2,6-Di-tert-butyl-4-Nitrophenol (DBNP). *Applied Occupational and Environmental Hygiene* **16** (4), 487–495. <https://doi.org/10.1080/10473220117206>.
- Al-Juboori, R. A. & Yusaf, T. 2012 Biofouling in RO system: mechanisms, monitoring and controlling. *Desalination* **302**, 1–23. <https://doi.org/10.1016/j.desal.2012.06.016>.
- Amjad, Z. 1993 *Reverse Osmosis: Membrane Technology, Water Chemistry and Industrial Application*. Van Nostrand Reinhold, New York, NY, USA.
- Amjad, Z. & Demadis, K. 2015 *Mineral Scales and Deposits: Scientific and Technological Approaches*. Elsevier, Amsterdam, the Netherlands.
- Andrews, J. M. 2001 Determination of minimum inhibitory concentrations. *Journal of Antimicrobial Chemotherapy* **48** (S1), 5–16. https://doi.org/10.1093/jac/48.suppl_1.5.
- Arikishnan, R. & Rajendran, N. 2021 Research trends in water scarcity: a world perspective. *Library Philosophy and Practice* **4819**, 1–9.
- Badenhorst, C. P. S., Erasmus, E., van der Sluis, R., Nortje, C. & van Dijk, A. A. 2014 A new perspective on the importance of glycine conjugation in the metabolism of aromatic acids. *Drug Metabolism Reviews* **46** (3), 343–361. <https://doi.org/10.3109/03602532.2014.908903>.
- Baker, J. S. & Dudley, L. Y. 1998 Biofouling in membrane systems – a review. *Desalination* **118** (1), 81–89. [https://doi.org/10.1016/S0011-9164\(98\)00091-5](https://doi.org/10.1016/S0011-9164(98)00091-5).
- Barraud, N., Hassett, D. J., Hwang, S., Rice, S. A., Kjelleberg, S. & Webb, J. S. 2006 Involvement of nitric oxide in biofilm dispersal of *Pseudomonas aeruginosa*. *Journal of Bacteriology* **188** (21), 7344–7353. <https://doi.org/10.1128/JB.00779-06>.
- Barraud, N., Storey, M. V., Moore, Z. P., Webb, J. S., Rice, S. A. & Kjelleberg, S. 2009 Nitric oxide-mediated dispersal in single- and multi-species biofilms of clinically and industrially relevant microorganisms. *Microbial Biotechnology* **2** (3), 370–378. <https://doi.org/10.1111/j.1751-7915.2009.00098.x>.
- Bates, W. T. 1998 Reducing the fouling rate of surface and wastewater RO systems. In *Proceedings of the 59th International Water Conference*, October 1998, Pittsburgh, PA, USA.
- Bertheas, U., Majamaa, K., Arzu, A. & Pahnke, R. 2009 Use of DBNPA to control biofouling in RO systems. *Desalination and Water Treatment* **3** (1–3), 175–178. <https://doi.org/10.5004/dwt.2009.457>.
- Blanchard, F. A., Gonsior, S. J. & Hopkins, D. L. 1987 2, 2-Dibromo-3-nitropropionamide (DBNPA) chemical degradation in natural waters: experimental evaluation and modeling of competitive pathways. *Water Research* **21** (7), 801–807. [https://doi.org/10.1016/0043-1354\(87\)90155-2](https://doi.org/10.1016/0043-1354(87)90155-2).

- Bott, T. R. 1998 Techniques for reducing the amount of biocide necessary to counteract the effects of biofilm growth in cooling water systems. *Applied Thermal Engineering* **18** (11), 1059–1066. [https://doi.org/10.1016/S1359-4311\(98\)00017-9](https://doi.org/10.1016/S1359-4311(98)00017-9).
- Bourke, S. J., Convery, R. P., Stenton, S. C., Malcolm, R. M. & Hendrick, D. J. 1997 Occupational asthma in an isothiazolinone manufacturing plant. *Thorax* **52** (8), 746. <http://doi.org/10.1136/thx.52.8.746>.
- Bridier, A., Briandet, R., Thomas, V. & Dubois-Brissonnet, F. 2011 Resistance of bacterial biofilms to disinfectants: a review. *Biofouling* **27** (9), 1017–1032. <https://doi.org/10.1080/08927014.2011.626899>.
- Buckley, H. L., Hart-Cooper, W. M., Kim, J. H., Faulkner, D. M., Cheng, L. W., Chan, K. L., Vulpe, C. D., Orts, W. J., Amrose, S. E. & Mulvihill, M. J. 2017 Design and testing of safer, more effective preservatives for consumer products. *ACS Sustainable Chemistry & Engineering* **5** (5), 4320–4331. <https://doi.org/10.1021/acssuschemeng.7b00374>.
- Bucs, S. S., Farhat, N., Kruithof, J. C., Picioreanu, C., van Loosdrecht, M. C. & Vrouwenvelder, J. S. 2018 Review on strategies for biofouling mitigation in spiral wound membrane systems. *Desalination* **434** (SI), 189–197. <https://doi.org/10.1016/j.desal.2018.01.023>.
- Budavari, S., O'Neil, M. J., Smith, A. & Heckelman, P. E. 1989 *The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals*. Merck & Co., Rahway, NJ, USA.
- Burnett, C. L., Bergfeld, W. F., Belsito, D. V., Klaassen, C. D., Marks, J. G., Shank, R. C., Slaga, T. J., Snyder, P. W. & Andersen, F. A. 2010 Final report of the safety assessment of methylisothiazolinone. *International Journal of Toxicology* **29** (S4), 187S–213S. <https://doi.org/10.1177/1091581810374651>.
- Campa, M. F., Techtmann, S. M., Ladd, M. P., Yan, J., Patterson, M., Amaral, A. G. D., Carter, K. E., Ulrich, N., Grant, C. J., Hettich, R. L., Lamendella, R. & Hazen, T. C. 2019 Surface water microbial community response to the biocide 2,2-dibromo-3-nitropropionamide, used in unconventional oil and gas extraction. *Applied and Environmental Microbiology* **85** (21). <https://doi.org/10.1128/AEM.01336-19>.
- Canavez, A. D. P. M., Corrêa, G. O. P., Isaac, V. L. B., Schuck, D. C. & Lorencini, M. 2021 Integrated approaches to testing and assessment as a tool for the hazard assessment and risk characterization of cosmetic preservatives. *Journal of Applied Toxicology* 1–13. <https://doi.org/10.1002/jat.4156>.
- Chapman, J. S. 2003 Biocide resistance mechanisms. *International Biodeterioration & Biodegradation* **51** (2), 133–138. [https://doi.org/10.1016/S0964-8305\(02\)00097-5](https://doi.org/10.1016/S0964-8305(02)00097-5).
- Chapman, J. S. & Diehl, M. A. 1995 Methylchloroisothiazolone-induced growth inhibition and lethality in *Escherichia coli*. *Journal of Applied Bacteriology* **78** (2), 134–141. <https://doi.org/10.1111/j.1365-2672.1995.tb02833.x>.
- Chen, F. 2012 The chronic aquatic toxicity of a microbicide dibromonitropropionamide. *Toxicology and Industrial Health* **28** (2), 181–185. <https://doi.org/10.1177/0748233711410904>.
- Chen, H. & Zhong, Q. 2018 Antibacterial activity of acidified sodium benzoate against *Escherichia coli* o157:H7, *Salmonella enterica*, and *Listeria monocytogenes* in tryptic soy broth on cherry tomatoes. *International Journal of Food Microbiology* **274**, 38–44. <https://doi.org/10.1016/j.jfoodmicro.2018.03.017>.
- Chipley, J. R., Davidson, P. M., Sofos, J. N. & Branen, A. L. 2020 Sodium benzoate and benzoic acid. In: *Antimicrobials in Food*, 4th edn. (Chipley, J. R. ed.). CRC Press, Boca Raton, FL, USA, pp. 11–48.
- Clean Production Action (CPA) 2016 2-Phenoxyethanol (CAS #122-99-6) GreenScreen® for. Available from: https://storage.googleapis.com/scsc_chem/122-99-6_2-Phenoxyethanol_GS-518_v1-2_Certified_Feb_2016_EDF.pdf (accessed 4 July 2021).
- Cloete, T. E., Jacobs, L. & Brözel, V. S. 1998 The chemical control of biofouling in industrial water systems. *Biodegradation* **9** (1), 23–37. <https://doi.org/10.1023/A:1008216209206>.
- CLSI-M02 2018 *Performance Standards for Antimicrobial Disk Susceptibility Tests – CLSI Standard M02*, 13th edn. Clinical and Laboratory Standards Institute, Wayne, PA, USA.
- CLSI-M07 2018 *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – CLSI Standard M07*, 11th edn. Clinical and Laboratory Standards Institute, Wayne, PA, USA.
- CLSI-M11 2018 *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria – CLSI Standard M11*, 9th edn. Clinical and Laboratory Standards Institute, Wayne, PA, USA.
- CLSI-M100 2021 *Performance Standards for Antimicrobial Susceptibility Testing – CLSI Supplement M100*, 31st edn. Clinical and Laboratory Standards Institute, Wayne, PA, USA.
- Code of Federal Regulations – United States Food and Drug Administration (CFR) 2020 Title 21 – Food and drugs. Available from: <https://www.govinfo.gov/content/pkg/CFR-2020-title21-vol3/pdf/CFR-2020-title21-vol3.pdf> (accessed 4 July 2021).
- Collier, P. J., Ramsey, A., Waigh, R. D., Douglas, K. T., Austin, P. & Gilbert, P. 1990 Chemical reactivity of some isothiazolone biocides. *Journal of Applied Bacteriology* **69** (4), 578–584. <https://doi.org/10.1111/j.1365-2672.1990.tb01551.x>.
- Cosmetic Ingredient Review (CIR) 1990 Final report on the safety assessment of phenoxyethanol. *Journal of the American College of Toxicology* **9** (2), 259–277. <https://doi.org/10.3109/10915819009078737>.
- Cosmetic Ingredient Review (CIR) 2001 Final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate. *International Journal of Toxicology* **20** (3), 23–50. <https://doi.org/10.1080/10915810152630729>.
- Crow, W. D. & Leonard, N. J. 1964 A synthesis of 3-isothiazolones. *Tetrahedron Letters* **5** (23), 1477–1480. [https://doi.org/10.1016/S0040-4039\(01\)89515-0](https://doi.org/10.1016/S0040-4039(01)89515-0).
- Cunningham, M. A., Ho, L. L., Nguyen, D. T., Gillilan, R. E. & Bash, P. A. 1997 Simulation of the enzyme reaction mechanism of malate dehydrogenase. *Biochemistry* **36** (16), 4800–4816. <https://doi.org/10.1021/bi962734n>.

- Curtin, A. 2020 *Mitigating Biofouling on Reverse Osmosis Membranes via Greener Preservatives*. MSc Thesis, the University of Victoria, Victoria, BC, Canada. Available from: <http://dspace.library.uvic.ca/handle/1828/12101?show=full> (accessed 19 July 2021).
- Curtin, A. M., Thibodeau, M. C. & Buckley, H. L. 2021 Anti-biofouling efficacy of three home and personal care product preservatives: *Pseudomonas aeruginosa* biofilm inhibition and prevention. *Biofouling* **37** (8), 879–893. <https://doi.org/10.1080/08927014.2021.1978988>.
- Danish Environmental Protection Agency (DEPA) 2015 *Survey and Health and Environmental Assessment of Preservatives in Cosmetic Products*. Available from: <https://www2.mst.dk/Udgiv/publications/2015/05/978-87-93352-19-3.pdf> (accessed 1 July 2021).
- Daulisio, M. D. C. Z. & Schneider, R. P. 2020 Inactivation of *Pseudomonas aeruginosa* MDC by isothiazolones and biocide stabilizing agents. *International Biodeterioration & Biodegradation* **155**, 105090. <https://doi.org/10.1016/j.ibiod.2020.105090>.
- Dow 2011 *Water & Process Solutions. FilmTec™ Reverse Osmosis Membranes Technical Manual*. Available from: <https://www.filterwater.com/docs/filmtec/dow-filmtec-ro-membranes-technical-manual-609416.pdf> (accessed 14 July 2021).
- Dréno, B., Zuberbier, T., Gelmetti, C., Gontijo, G. & Marinovich, M. 2019 Safety review of phenoxyethanol when used as a preservative in cosmetics. *Journal of the European Academy of Dermatology and Venereology* **33** (S7), 15–24. <https://doi.org/10.1111/jdv.15944>.
- Dudley, L. Y. & Darton, E. G. 1997 Pretreatment procedures to control biogrowth and scale formation in membrane systems. *Desalination* **110** (1–2), 11–20. [https://doi.org/10.1016/S0011-9164\(97\)00080-5](https://doi.org/10.1016/S0011-9164(97)00080-5).
- Dupont 2021 *FilmTec™ Reverse Osmosis Membranes Technical Manual*. Available from: <https://www.dupont.com/content/dam/dupont/amer/us/en/water-solutions/public/documents/en/45-D01504-en.pdf> (accessed 8 July 2021).
- Eachus, A. C. & Pohlman, J. L. 2004 Applications of 2, 2-Dibromo-3-nitropropionamide (DBNPA), a non-traditional antimicrobial agent, in metalworking fluid production and use. *Tribology & Lubrication Technology* **60** (12), 42.
- EFSA Panel on Food Additives and Nutrient Sources Added to Food (EFSA ANS Panel). 2016 Scientific opinion on the re-evaluation of sulfur dioxide (E 220), sodium sulfite (E 221), sodium bisulfite (E 222), sodium metabisulfite (E 223), potassium metabisulfite (E 224), calcium sulfite (E 226), calcium bisulfite (E 227) and potassium bisulfite (E 228) as food additives. *EFSA Journal* **14** (4). <https://doi.org/10.2903/j.efsa.2016.4438>.
- Eke, J., Yusuf, A., Giwa, A. & Sodiq, A. 2020 The global status of desalination: an assessment of current desalination technologies, plants and capacity. *Desalination* **495**, 114633. <https://doi.org/10.1016/j.desal.2020.114633>.
- Er, B., Demirhan, B., Onurdağ, F. K., Özgacar, S. Ö. & Öktem, A. B. 2014 Antimicrobial and antibiofilm effects of selected food preservatives against *Salmonella* spp. isolated from chicken samples. *Poultry Science* **93** (3), 695–701. <https://doi.org/10.3382/ps.2013-03404>.
- European Chemicals Agency (ECHA). 2015 *REACH Dossier for 2-Phenoxyethanol (CAS# 122-99-6)*. Available from: <https://echa.europa.eu/registration-dossier/-/registered-dossier/15160/7/3/1> (accessed 2 July 2021).
- European Chemicals Agency (ECHA) 2018 *Opinion on the Application for Approval of the Active Substance: 2-Phenoxyethanol*. Available from: <https://echa.europa.eu/documents/10162/13ad12c5-feeac686-2e0c-84722c8d287d> (accessed 7 July 2021).
- European Chemicals Agency (ECHA) 2019 Opinion on the application for approval of the active substance 2,2-dibromo-2-cyanoacetamide (DBNPA). Available from: <https://echa.europa.eu/documents/10162/021c479b-18d7-4d41-ae23-7a92f4b16c77> (accessed 2 July 2021).
- Exner, J. H., Burk, G. A. & Kyriacou, D. 1973 Rates and products of decomposition of 2, 2-dibromo-3-nitropropionamide. *Journal of Agricultural and Food Chemistry* **21** (5), 838–842. <https://doi.org/10.1021/jf60189a012>.
- Fane, T. 2015 Irreversible fouling. In: *Encyclopedia of Membranes* (Drioli, E. & Giorno, L., eds). Springer, Berlin/Heidelberg, Germany. https://doi.org/10.1007/978-3-642-40872-4_328-1.
- Fazel, M. & Darton, E. D. 2001 A statistical review of 150 membrane autopsies. In: *Proceedings of the 62nd Annual International Water Conference*, October 2001, Pittsburgh, PA, USA.
- Feiner, G. 2006 *Meat Products Handbook: Practical Science and Technology*. Woodhead Publishing Limited, Abington Hall, Abington, Cambridge, UK.
- Ferreira, C., Rosmaninho, R., Simões, M., Pereira, M. C., Bastos, M. M. S. M., Nunes, O. C. & Melo, L. F. 2009 Biofouling control using microparticles carrying a biocide. *Biofouling* **26** (2), 205–212. <https://doi.org/10.1080/08927010903419630>.
- Fitzgerald, K. A., Davies, A. & Russell, A. D. 1992 Mechanism of action of chlorhexidine diacetate and phenoxyethanol singly and in combination against gram-negative bacteria. *Microbios* **70** (284–285), 215–230.
- Flemming, H. C. 1997 Reverse osmosis membrane biofouling. *Experimental Thermal and Fluid Science* **14** (4), 382–391. [https://doi.org/10.1016/S0894-1777\(96\)00140-9](https://doi.org/10.1016/S0894-1777(96)00140-9).
- Frank, K. L. & Patel, R. 2007 Activity of sodium metabisulfite against planktonic and biofilm *Staphylococcus* species. *Diagnostic Microbiology and Infectious Disease* **57** (4), 355–359. <https://doi.org/10.1016/j.diagmicrobio.2006.10.003>.
- Frayne, C. 2001 The selection and application of nonoxidizing biocides for cooling water systems. *The Analyst*, 1–10. Available from: <http://scalinguph2o.com/wp-content/uploads/2017/10/biocide-1.pdf> (accessed 19 July 2021).
- García-Gavín, J., Parente, J. & Goossens, A. 2012 Allergic contact dermatitis caused by sodium metabisulfite: a challenging allergen. A case series and literature review. *Contact Dermatitis* **67** (5), 260–269. <https://doi.org/10.1111/j.1600-0536.2012.02135.x>.
- Gilbert, P., Beveridge, E. G. & Crone, P. B. 1977 Effect of phenoxyethanol on the permeability of *Escherichia coli* Nctc 5933 to inorganic ions. *Microbios* **19** (75), 17–26.
- Gillings, M. R. 2010 Biocide use, integrons and novel genetic elements. *Microbiology Australia* **31** (4), 192. <https://doi.org/10.1071/MA10192>.

- Gomes, L. C., Araújo, P. A., Teodósio, J. S., Simões, M. & Mergulhão, F. J. 2014 The effect of plasmids and other biomolecules on the effectiveness of antibiofilm agents. In: *Antibiofilm Agents* (Rumbaugh, K. & Ahmad, I., eds). Springer, Berlin/Heidelberg, Germany. https://doi.org/10.1007/978-3-642-53833-9_8.
- Gomes, I. B., Lemos, M., Fernandes, S., Borges, A., Simões, L. C. & Simões, M. 2021 The effects of chemical and mechanical stresses on *Bacillus cereus* and *Pseudomonas fluorescens* single- and dual-species biofilm removal. *Microorganisms* **9** (6), 1174. <https://doi.org/10.3390/microorganisms9061174>.
- Gosselin, R. E., Hodge, H. C., Smith, R. P. & Gleason, M. N. 1976 *Clinical Toxicology of Commercial Products*, 4th edn. Williams and Wilkins, Baltimore, MD, USA, 4–123.
- Grant, D. M. & Bott, T. R. 2005 Biocide dosing strategies for biofilm control. *Heat Transfer Engineering* **26** (1), 44–50. <https://doi.org/10.1080/01457630590890166>.
- Grecka, K. & Szweda, P. 2021 Synergistic effects of propolis combined with 2-phenoxyethanol and antipyretics on the growth of *Staphylococcus aureus*. *Pharmaceutics* **13** (2), 215. <https://doi.org/10.3390/pharmaceutics13020215>.
- GreenScreen for Safer Chemicals (GSC) 2021 *GreenScreen For Safer Chemicals*. Available from: <https://www.greenscreenchemicals.org/learn/full-greenscreen-method> (accessed 13 July 2021).
- Gude, V. G. 2017 Desalination and water reuse to address global water scarcity. *Reviews in Environmental Science and Bio/Technology* **16** (4), 591–609. <https://doi.org/10.1007/s11157-017-9449-7>.
- Güven, N. & Onurdağ, F. K. 2014 Investigation of antimicrobial and antibiofilm effects of some preservatives used in drugs, cosmetics and food products. *Microbiology Bulletin* **48** (1), 94–105.
- Häberle, M., Geier, J. & Mahler, V. 2016 Contact allergy to sulfites: clinical and occupational relevance – new data from the German contact dermatitis research group and the information network of departments of dermatology (IVDK). *Journal of the German Dermatological Society* **14** (9), 938–941. <https://doi.org/10.1111/ddg.13009>.
- Hall, A. L. & Al, H. 1981 Phenoxyethanol. A cosmetically acceptable preservative. *Cosmetics & Toiletries* **96**, 83–85.
- Haque, H., Cutright, T. J. & Newby, B. Z. 2005 Effectiveness of sodium benzoate as a freshwater low toxicity antifoulant when dispersed in solution and entrapped in silicone coatings. *Biofouling* **21** (2), 109–119. <https://doi.org/10.1080/08927010500222551>.
- Hawkins, D. R., Rocabayera, X., Ruckman, S., Segret, R. & Shaw, D. 2009 Metabolism and pharmacokinetics of ethyl N^α-lauroyl-L-arginate hydrochloride in human volunteers. *Food and Chemical Toxicology* **47** (11), 2711–2715. <https://doi.org/10.1016/j.fct.2009.07.028>.
- Hawley, G. G. 1971 *The Condensed Chemical Dictionary*, 8th edn. Van Nostrand Reinhold, New York, NY, USA.
- Haynes, W. M. 2010 *CRC Handbook of Chemistry and Physics*. CRC Press, Boca Raton, FL, USA, pp. 3–522.
- Hegstad, K., Langsrud, S., Lunestad, B. T., Scheie, A. A., Sunde, M. & Yazdankhah, S. P. 2010 Does the wide use of quaternary ammonium compounds enhance the selection and spread of antimicrobial resistance and thus threaten our health? *Microbial Drug Resistance* **16** (2), 91–104. <https://doi.org/10.1089/mdr.2009.0120>.
- Hesse, B. C. 1896 *On Malonic Nitrile and Some of its Derivatives...* Chemical Publishing Company, Easton, PA, USA.
- Hetrick, E. M., Shin, J. H., Stasko, N. A., Johnson, C. B., Wespe, D. A., Holmuhamedov, E. & Schoenfish, M. H. 2008 Bactericidal efficacy of nitric oxide-releasing silica nanoparticles. *ACS Nano* **2** (2), 235–246. <https://doi.org/10.1021/nn700191f>.
- Hoeck, E. 2017 *Reverse Osmosis Membrane Biofouling: Causes, Consequences and Countermeasures*. Available from: http://www.aquamem.com/publications/WPI_RO-Biofouling_WhitePaper_v1_4-24-17.pdf (accessed 1 July 2021).
- Husson, M., Schiff, M., Foulhoux, A., Cano, A., Dobbelaere, D., Brassier, A., Mention, K., Arnoux, J., Feillet, F., Chabrol, B., Guffon, N., Elie, C. & de Lonay, P. 2016 Efficacy and safety of i.v. sodium benzoate in urea cycle disorders: a multicentre retrospective study. *Orphanet Journal of Rare Diseases* **127**, 11. <https://doi.org/10.1186/s13023-016-0513-0>.
- Hydranautics Nitto Group Company (HNGC) 2015 Technical service bulletin. Available from: <https://membranes.com/docs/tsb/TSB110.pdf> (accessed 1 July 2021).
- Irwin, S. V., Fisher, P., Graham, E., Malek, A. & Robidoux, A. 2017 Sulfites inhibit the growth of four species of beneficial gut bacteria at concentrations regarded as safe for food. *PLoS One* **12** (10), e0186629–e0186629. <https://doi.org/10.1371/journal.pone.0186629>.
- Ivniisky, H., Katz, I., Minz, D., Shimoni, E., Chen, Y., Tarchitzky, J., Semiat, R. & Dosoretz, C. G. 2005 Characterization of membrane biofouling in nanofiltration processes of wastewater treatment. *Desalination* **185** (1–3), 255–268. <https://doi.org/10.1016/j.desal.2005.03.081>.
- Japan Bioassay Research Center (JBRC) 2007 *Summary of Drinking Water Carcinogenicity Study of 2-Phenoxyethanol in F344 Rats*. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/2-Phenoxyethanol_Rats.pdf (accessed 15 July 2021).
- Johnson Jr., W., Bergfeld, W. F., Belsito, D. V., Hill, R. A., Klaassen, C. D., Liebler, D. C., Marks, J. G., Shank, T. J., Slaga, T. J., Snyder, P. W. & Andersen, F. A. 2017 Safety assessment of benzyl alcohol, benzoic acid and its salts, and benzyl benzoate. *International Journal of Toxicology* **36** (3), 5S–30S. <https://doi.org/10.1177/1091581817728996>.
- Kabara, J. J. 1984 *Cosmetic and Drug Preservation: Principles and Practice*, 1st edn. Marcel Dekker, New York, NY, USA, pp. 79–108.
- Karabay, O. & Sahin, I. 2005 *In vitro* activity of sodium-benzoate against isolates of methicillin-resistant *Staphylococcus aureus*. *West Indian Medical Journal* **54** (2), 107–109.
- Karabay, O., Kocoglu, E., Ince, N., Sahan, T. & Ozdemir, D. 2006 *In vitro* activity of sodium benzoate against clinically relevant *Enterococcus faecalis* and *Enterococcus faecium* isolates. *The Journal of Microbiology* **44** (1), 129–131.
- Kim, Y. & Choi, J. 2019 Early life exposure of a biocide, CMIT/MIT causes metabolic toxicity via the O-GlcNAc transferase pathway in the nematode *C. elegans*. *Toxicology and Applied Pharmacology* **376**, 1–8. <https://doi.org/10.1016/j.taap.2019.05.012>.

- Kim, T. & Park, H. 2015 Tributyl tetradecyl phosphonium chloride for biofouling control in reverse osmosis processes. *Desalination* **372**, 39–46. <https://doi.org/10.1016/j.desal.2015.06.019>.
- Kim, T. & Park, H. 2016 Lauroyl arginate ethyl: an effective antibiofouling agent applicable for reverse osmosis processes producing potable water. *Journal of Membrane Science* **507**, 24–33. <https://doi.org/10.1016/j.memsci.2016.01.056>.
- Kim, H. R., Lee, K., Park, C. W., Song, J. A., Shin, D. Y., Park, Y. J. & Chung, K. H. 2016 Polyhexamethylene guanidine phosphate aerosol particles induce pulmonary inflammatory and fibrotic responses. *Archives of Toxicology* **90** (3), 617–632. <https://doi.org/10.1007/s00204-015-1486-9>.
- Kim, M. K., Kim, K. B., Lee, J. Y., Kwack, S. J., Kwon, Y. C., Kang, J. S., Kim, H. S. & Lee, B. M. 2019 Risk assessment of 5-chloro-2-methylisothiazol-3 (2H)-one/2-methylisothiazol-3 (2H)-one (CMIT/MIT) used as a preservative in cosmetics. *Toxicological Research* **35** (2), 103–117. <https://doi.org/10.5487/TR.2019.35.2.103>.
- Kimura, T. & Nishioka, H. 1997 Intracellular generation of superoxide by copper sulphate in *Escherichia coli*. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* **389** (2–3), 237–242. [https://doi.org/10.1016/S1383-5718\(96\)00153-2](https://doi.org/10.1016/S1383-5718(96)00153-2).
- Kolaei, E. A., Tweddell, R. J. & Avis, T. J. 2012 Antifungal activity of sulfur-containing salts against the development of carrot cavity spot and potato dry rot. *Postharvest Biology and Technology* **63** (1), 55–59. <https://doi.org/10.1016/j.postharvbio.2011.09.006>.
- Kramer, J. F. & Tracey, D. A. 1995 The solution to reverse osmosis biofouling. In *Proceedings of IDA World Congress on Desalination and Water Use*, November 1995, Abu Dhabi, Saudi Arabia.
- Krebs, H. A., Wiggins, D. & Stubbs, M. 1983 Studies on the mechanism of the antifungal action of benzoate. *Biochemical Journal* **241** (3), 657–663. <https://doi.org/10.1042/bj2140657>.
- Kucera, J. 2010 *Reverse Osmosis: Design, Processes, and Applications for Engineers*, 1st edn. Scrivener Publishing LLC, Salem, MA, USA.
- Kucera, J. 2015 *Reverse Osmosis: Design, Processes, and Applications for Engineers*, 2nd edn. Scrivener Publishing LLC, Salem, MA, USA.
- Kucera, J. 2019 Biofouling of polyamide membranes: fouling mechanisms, current mitigation and cleaning strategies, and future prospects. *Membranes* **9** (9). <https://doi.org/10.3390/membranes9090111>.
- L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (National Agency for the Safety of Medicines and Health Products) (NASMHP). 2019 *Les produits cosmétiques non rincés contenant du phénoxyéthanol ne doivent pas être utilisés sur les fesses des enfants de 3 ans ou moins – Point d'Information (Leave-on Cosmetics Containing Phenoxyethanol Should Not Be Used on the Buttocks of Children 3 Years of Age or Younger)*. Available from: <https://ansm.sante.fr/actualites/concentration-de-phenoxyethanol-dans-les-produits-cosmetiques-information-actualisee> (accessed 1 July 2021).
- Lane, H. Y., Lin, C. H., Green, M. F., Helleman, G., Huang, C. C., Chen, P. W., Tun, R., Chang, Y. C. & Tsai, G. C. E. 2013 Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. *JAMA Psychiatry* **70** (12), 1267–1275. <https://doi.org/10.1001/jamapsychiatry.2013.2159>.
- Lee, E., Son, S. K., Yoon, J., Cho, H. J., Yang, S. I., Jung, S., Do, K. H., Cho, Y. A., Lee, S. Y., Park, D. U. & Hong, S. J. 2018 Two cases of chloromethylisothiazolinone and methylisothiazolinone-associated toxic lung injury. *Journal of Korean Medical Science* **33** (16), e119. <https://doi.org/10.3346/jkms.2018.33.e119>.
- Lennerz, B. S., Vafai, S. B., Delaney, N. F., Clish, C. B., Deik, A. A., Pierce, K. A., Ludwig, D. S. & Mootha, V. K. 2015 Effects of sodium benzoate, a widely used food preservative, on glucose homeostasis and metabolic profiles in humans. *Molecular Genetics and Metabolism* **114** (1), 73–79. <http://doi.org/10.1016/j.ymgme.2014.11.010>.
- Li, A., Wu, Q. Y., Tian, G. P. & Hu, H. Y. 2016 Effective degradation of methylisothiazolone biocide using ozone: kinetics, mechanisms, and decreases in toxicity. *Journal of Environmental Management* **183** (3), 1064–1071. <https://doi.org/10.1016/j.jenvman.2016.08.057>.
- Lilienblum, W. 2016 Opinion of the Scientific Committee on Consumer Safety (SCCS) – Final version of the opinion on phenoxyethanol in cosmetic products. *Regulatory Toxicology and Pharmacology* **82**, 156. <https://doi.org/10.1016/j.yrtph.2016.11.007>.
- Liu, F., Chang, X., Yang, F., Wang, Y., Wang, F., Dong, W. & Zhao, C. 2011 Effect of oxidizing and non-oxidizing biocides on biofilm at different substrate levels in the model recirculating cooling water system. *World Journal of Microbiology and Biotechnology* **27** (12), 2989–2997. <https://doi.org/10.1007/s11274-011-0783-6>.
- Liu, X., Li, Z., Fan, Y., Lekbach, Y., Song, Y., Xu, D., Zhang, Z., Ding, L. & Wang, F. 2020 A mixture of d-amino acids enhances the biocidal efficacy of CMIT/MIT against corrosive *Vibrio harveyi* biofilm. *Frontiers in Microbiology* **11**, 557435. <https://doi.org/10.3389/fmicb.2020.557435>.
- Lundov, M. D. 2010 *Methylisothiazolinone: Contact Allergy and Antimicrobial Efficacy*. PhD Thesis, National Allergy Research Centre, University of Copenhagen, Copenhagen, Denmark.
- Lyman, W. J., Reehl, W. F. & Rosenblatt, D. H. 1990 *Handbook of Chemical Property Estimation Methods*. American Chemical Society, Washington, DC, USA.
- Macedo, L. L., Da Silva Araújo, C., Vimercati, W. C., Saraiva, S. H. & Teixeira, L. J. Q. 2019 Evaluation of different bleaching methods applied to Yacon. *Journal of Food Process Engineering* **42** (7). <https://doi.org/10.1111/jfpe.13276>.
- Macià, M. D., Rojo-Molinero, E. & Oliver, A. 2014 Antimicrobial susceptibility testing in biofilm-growing bacteria. *Clinical Microbiology and Infection* **20** (10), 981–990. <https://doi.org/10.1111/1469-0691.12651>.
- Mácová, S., Doleželová, P., Pisteková, V., Svobodová, Z., Bedanova, I. & Voslarova, E. 2008 Comparison of acute toxicity of 2-phenoxyethanol and clove oil to juvenile and embryonic stages of Danio rerio. *Neuroendocrinology Letters* **29** (5), 680.
- Madan, V., Walker, S. L. & Beck, M. H. 2007 Sodium metabisulfite allergy is common but is it relevant? *Contact Dermatitis* **57** (3), 173–176. <https://doi.org/10.1111/j.1600-0536.2007.01188.x>.

- Majamaa, K., Bertheas, U., Finlayson, F. & Levy, R. B. 2011 Preservation of reverse osmosis membranes with non oxidizing biocides – comparison with SMBS. *Water Supply* **11** (3), 342–351. <https://doi.org/10.2166/ws.2011.041>.
- Mathurin, Y. K., Koffi-Nevry, R., Guéhi, S. T., Tano, K. & Oulé, M. K. 2012 Antimicrobial activities of polyhexamethylene guanidine-based disinfectant against fungi isolated from cocoa beans and reference strains of bacteria. *Journal of Food Protection* **75** (6), 1167–1171. <https://doi.org/10.4315/0362-028X.JFP-11-361>.
- Mayes, M. A., Blanchard, F. A., Hopkins, D. L. & Takahashi, I. T. 1985 Static acute toxicity of dibromonitropropionamide and selected degradation products to the fathead minnow (*Pimephales promelas* Rafinesque). *Environmental Toxicology and Chemistry* **4** (6), 823–830. <https://doi.org/10.1002/etc.5620040613>.
- Min, J., Chen, W. & Hu, X. 2019 Biodegradation of 2,6-dibromo-4-nitrophenol by *Cupriavidus* sp. strain CNP-8: kinetics, pathway, genetic and biochemical characterization. *Journal of Hazardous Materials* **361**, 10–18. <https://doi.org/10.1016/j.jhazmat.2018.08.063>.
- Mohammad, A. W. & Ali, N. 2002 Understanding the steric and charge contributions in NF membranes using increasing MWCO polyamide membranes. *Desalination* **147** (1–3), 205–212. [https://doi.org/10.1016/S0011-9164\(02\)00535-0](https://doi.org/10.1016/S0011-9164(02)00535-0).
- Morley, J. O., Kapur, A. J. O. & Charlton, M. H. 2005 Structure–activity relationships in 3-isothiazolones. *Organic & Biomolecular Chemistry* **3** (20), 3713–3719. <https://doi.org/10.1039/b509529h>.
- Munla, L., Peldszus, S. & Huck, P. M. 2012 Reversible and irreversible fouling of ultrafiltration ceramic membranes by model solutions. *American Water Works Association* **104** (10), E540–E554. <https://doi.org/10.5942/jawwa.2012.104.0137>.
- Murano, A., Morinaga, N., Iwamaru, Y., Yahiro, K., Tagashira, M., Moss, J., Tanzawa, H. & Noda, M. 2005 Acidic conditions enhance bactericidal effects of sodium bisulfite on *Helicobacter pylori*. *Helicobacter* **10** (2), 132–135. <https://doi.org/10.1111/j.1523-5378.2005.00299.x>.
- Nagaraja, N., Skillman, L., Xie, Z., Jiang, S., Ho, G. & Li, D. 2017 Investigation of compounds that degrade biofilm polysaccharides on reverse osmosis membranes from a full scale desalination plant to alleviate biofouling. *Desalination* **403**, 88–96. <https://doi.org/10.1016/j.desal.2016.06.002>.
- Nair, B. & Elmore, A. R. & Cosmetic Ingredients Review Expert Panel 2003 Final report on the safety assessment of sodium sulfite, potassium sulfite, ammonium sulfite, sodium bisulfite, ammonium bisulfite, sodium metabisulfite and potassium metabisulfite. *International Journal of Toxicology* **22**, 63–88. <https://doi.org/10.1080/10915810390239478>.
- Nguyen, T., Roddick, F. A. & Fan, L. 2012 Biofouling of water treatment membranes: a review of the underlying causes, monitoring techniques and control measures. *Membranes* **2** (4), 804–840. <https://doi.org/10.3390/membranes2040804>.
- Oh, H., Constancias, F., Ramasamy, C., Tang, P. Y., Yee, M. O., Fane, A., McDougald, D. & Rice, S. 2018 Biofouling control in reverse osmosis by nitric oxide treatment and its impact on the bacterial community. *Journal of Membrane Science* **550**, 313–321. <https://doi.org/10.1016/j.memsci.2018.01.012>.
- Ohara, H., Watanabe, M., Takebayashi, M., Abe, S., Matsuzaki, T. & Hayasaka, M. 2020 Bactericidal and antiproliferative effects of peripheral parenteral nutrition solutions with sodium bisulfite on pathogenic microorganisms in catheter lumens. *International Journal of Medical Sciences* **17** (12), 1833–1839. <https://doi.org/10.7150/ijms.48829>.
- Oliphant, T., Mitra, A. & Wilkinson, M. 2012 Contact allergy to sodium sulfite and its relationship to sodium metabisulfite. *Contact Dermatitis* **66** (3), 128–130. <https://doi.org/10.1111/j.1600-0536.2011.02029.x>.
- Ough, C. S. & Were, L. 2005 *Antimicrobials in Food*. CRC Taylor & Francis, Boca Raton, FL, USA, pp. 143–167.
- Oulé, M. K., Azinwi, R., Bernier, A., Kablan, T., Maupertuis, A., Mauler, S., Nevry, R. K., Dembélé, K., Forbes, L. & Diop, L. 2008 Polyhexamethylene guanidine hydrochloride-based disinfectant: a novel tool to fight methicillin-resistant *Staphylococcus aureus* and nosocomial infections. *Journal of Medical Microbiology* **57** (12), 1523–1528. <https://doi.org/10.1099/jmm.0.2008/003350-0>.
- Park, S. K. & Kwon, J. H. 2016 The fate of two isothiazolinone biocides, 5-chloro-2-methylisothiazol-3 (2H)-one (CMI) and 2-methylisothiazol-3 (2H)-one (MI), in liquid air fresheners and assessment of inhalation exposure. *Chemosphere* **144**, 2270–2276. <https://doi.org/10.1016/j.chemosphere.2015.10.136>.
- Park, H. S., Chatterjee, I., Dong, X., Wang, S., Sensen, C. W., Caffrey, S. M., Jack, T. R., Boivin, J. & Voordouw, G. 2011 Effect of sodium bisulfite injection on the microbial community composition in a brackish-water-transporting pipeline. *Applied and Environmental Microbiology* **77** (19), 6908–6917. <https://doi.org/10.1128/AEM.05891-11>.
- Park, D., Park, J., Yang, K. W., Park, J., Kwon, J. & Oh, H. B. 2020 Properties of polyhexamethylene guanidine (PHMG) associated with fatal lung injury in Korea. *Molecules* **25** (14), 3301–3312. <https://doi.org/10.3390/molecules25143301>.
- Paulus, W. 2005 *Directory of Microbicides for the Protection of Materials: A Handbook*. Springer, Dordrecht, The Netherlands.
- Pena, N., Gallego, S., Del Vigo, F. & Chesters, S. P. 2013 Evaluating impact of fouling on reverse osmosis membranes performance. *Desalination and Water Treatment* **51** (4–6), 958–968. <https://doi.org/10.1080/19443994.2012.699509>.
- Penna, V. T. C., Martins, S. A. M. & Mazzola, P. G. 2002 Identification of bacteria in drinking and purified water during the monitoring of a typical water purification system. *BMC Public Health* **2** (1), 13–13. <https://doi.org/10.1186/1471-2458-2-13>.
- Pharos 2021 *Overview of GreenScreen Method*. Available from: <https://pharosproject.net/overview-of-greenscreen-method> (accessed 13 July 2021).
- Pilloni, A., Carere, M., Orru, G., Scano, A., Trezza, C., Rojas, M. A. & Zeza, B. 2018 Adjunctive use of an ethyl lauroyl arginate-(LAE)-containing mouthwash in the nonsurgical therapy of periodontitis: a randomized clinical trial. *Minerva Stomatologica* **67** (1), 1–11. <https://doi.org/10.23736/S0026-4970.17.04084-5>.
- Poudrier, J. K. 1990 Final report on the safety assessment of phenoxyethanol. *Journal of the American College of Toxicology* **9** (2), 259–277.

- Puschmann, J., Herbig, M. E. & Müller-Goymann, C. C. 2018 Correlation of antimicrobial effects of phenoxyethanol with its free concentration in the water phase of o/w-emulsion gels. *European Journal of Pharmaceutics and Biopharmaceutics* **131**, 152–161. <https://doi.org/10.1016/j.ejpb.2018.08.007>.
- Qualley, A. V., Widhalm, J. R., Adebessin, F., Kish, C. M. & Dudareva, N. 2012 Completion of the core beta-oxidative pathway of benzoic acid biosynthesis in plants. *Proceedings of the National Academy of Sciences in the United States of America* **109** (40), 16383–16388. <https://doi.org/10.1073/pnas.1211001109>.
- Ras, G. R. 2016 *Control of Biofouling on Reverse Osmosis Membranes Using DBNPA*. MEng Thesis, Stellenbosch University, Stellenbosch, South Africa.
- Redondo, J. A. & Lomax, I. 2001 Y2 K generation FILMTEC RO membranes combined with new pretreatment techniques to treat raw water with high fouling potential: summary of experience. *Desalination* **136** (1), 287–306. [https://doi.org/10.1016/S0011-9164\(01\)00192-8](https://doi.org/10.1016/S0011-9164(01)00192-8).
- Roberts, D. W., Basketter, D., Kimber, I., White, J., McFadden, J. & White, I. R. 2012 Sodium metabisulfite as a contact allergen – an example of a rare chemical mechanism for protein modification. *Contact Dermatitis* **66** (3), 123–127. <https://doi.org/10.1111/j.1600-0536.2011.02038.x>.
- Ryon, M. G., Stewart, A. J., Kszos, L. A. & Phipps, T. L. 2002 Impacts on streams from the use of sulfur-based compounds for dechlorinating industrial effluents. *Water, Air, and Soil Pollution* **136** (1), 255–268. <https://doi.org/10.1023/A:1015264509699>.
- Sagoo, S. K., Board, R. & Roller, S. 2002 Chitosan potentiates the antimicrobial action of sodium benzoate on spoilage yeasts. *Letters in Applied Microbiology* **34** (3), 168–172. <https://doi.org/10.1046/j.1472-765x.2002.01067.x>.
- Santos, N. D., Azmat, S., Cuenca, Y., Drenth, J., Lauper, J. & Tseng, A. S. 2016 Effects of the biocide methylisothiazolinone on *Xenopus laevis* wound healing and tail regeneration. *Aquatic Toxicology* **181**, 37–45. <https://doi.org/10.1016/j.aquatox.2016.10.016>.
- Schook, P., Singleton, F., Patwardhan, R., Majarnaa, K., Summerfield, J., Sehn, P., Vance-Moeser, R. & Nanett, H. 2012 Biocidal control of biofouling of reverse osmosis, membrane systems. In: *Proceedings of the 73rd Annual International Water Conference*, November 2012, San Antonio, TX, USA.
- Scientific Committee on Consumer Products (SCCP) 2005 *Opinion on Benzoic Acid and Sodium Benzoate*. European Commission, Health & Consumer Protection Directorate C – Public Health and Risk Assessment, C7 – Risk assessment. SCCP/0891/05. SCCP, Brussels. Available from: <https://www.alegesanatos.ro/dbimg/files/Benzoic%20acid%20-%20Sodium%20benzoate.pdf> (accessed 15 July 2021).
- Siddiqui, A., Pinel, I., Prest, E. I., Bucs, S., Van Loosdrecht, M. C. M., Kruithof, J. C. & Vrouwenvelder, J. S. 2017 Application of DBNPA dosage for biofouling control in spiral wound membrane systems. *Desalination and Water Treatment* **68**, 12–22. <https://doi.org/10.5004/dwt.2017.20370>.
- Silva, V., Silva, C., Soares, P., Garrido, E. M., Borges, F. & Garrido, J. 2020 Isothiazolinone biocides: chemistry, biological, and toxicity profiles. *Molecules* **25** (4), 991. <https://doi.org/10.3390/molecules25040991>.
- Singh, R. 2015 Chapter 2 – water and membrane treatment. *Elsevier* **2**, 81–178. <https://doi.org/10.1016/B978-0-444-63362-0.00002-1>.
- Singh, A. K. 2021 An inclusive study on new conceptual designs of passive solar desalting systems. *Heliyon* **7**, 2. <https://doi.org/10.1016/j.heliyon.2020.e05793>.
- Singh, A. K. & Samsher. 2021a A review study of solar desalting units with evacuated tube collectors. *Journal of Cleaner Production* **279**, 123542. <https://doi.org/10.1016/j.jclepro.2020.123542>.
- Singh, A. K. & Samsher. 2021b Material conscious energy matrix and enviro-economic analysis of passive ETC solar still. In *2nd International Conference on Future Learning Aspects of Mechanical Engineering*, vol. 38, pp. 1–5. <https://doi.org/10.1016/j.matpr.2020.05.117>.
- Singh, A. K. & Samsher. 2021c Tech-en-econ-energy-exergy-matrix (T4EM) observations of evacuated solar tube collector augmented solar desalination unit: a modified design loom. *Materials Today: Proceedings*. <https://doi.org/10.1016/j.matpr.2021.09.088>.
- Singh, A. K., Yadav, R. K., Mishra, D., Prasad, R., Gupta, L. K. & Kumar, P. 2020 Active solar distillation technology: a wide overview. *Desalination* **493**, 114652. <https://doi.org/10.1016/j.desal.2020.114652>.
- Slawson, R. M., Lee, H. & Trevors, J. T. 1990 Bacterial interactions with silver. *Biology of Metals* **3** (3–4), 151–154. <https://doi.org/10.1007/BF01140573>.
- Sushma, S., Dasarthy, S., Tandon, R. K., Jain, S., Gupta, S. & Bhist, M. S. 1992 Sodium benzoate in the treatment of acute hepatic encephalopathy: a double-blind randomized trial. *Hepatology* **16** (1), 138–144. <https://doi.org/10.1002/hep.1840160123>.
- Tan, Y., Sun, L., Li, B., Zhao, X., Yu, T., Ikuno, N., Ishii, K. & Hu, H. 2017 Fouling characteristics and fouling control of reverse osmosis membranes for desalination of dyeing wastewater with high chemical oxygen demand. *Desalination* **419**, 1–7. <https://doi.org/10.1016/j.desal.2017.04.029>.
- United Nations Environment Programme (UNEP) 2004 *OECD SIDS – Ethylene Glycol Phenyl Ether* (CAS# 122-99-6). Paris, France. Available from: <https://hvpchemicals.oecd.org/UI/handler.axd?id=e38884d0-f1ef-4e8e-9373-fcdc44bf698b> (accessed 1 July 2021).
- United Nations – Water (UN-Water) 2021 *Summary Progress Update 2021: SDG 6 – Water and Sanitation for All*. Geneva, Switzerland. Available from: https://www.unwater.org/app/uploads/2021/02/SDG-6-Summary-Progress-Update-2021_Version-2021-03-03.pdf (accessed 7 July 2021).
- United States Food and Drug Administration (U.S. FDA) 2005 Agency Response Letter GRAS Notice No. GRN 000164. Silver Spring, MD, USA. Available from: <https://italisrl.com/wp-content/uploads/2016/05/GRAS-Notice-GRN-000164-Sept-2005.pdf> (accessed 1 July 2021).
- Vally, H. & Misso, N. L. 2012 Adverse reactions to the sulphite additives. *Gastroenterology and Hepatology From bed to Bench* **5** (1), 16.

- Vally, H., Misso, N. L. A. & Madan, V. 2009 Clinical effects of sulphite additives. *Clinical and Experimental Allergy* **39** (11), 1643–1651. <https://doi.org/10.1111/j.1365-2222.2009.03362.x>.
- Van Huizen, A. V., Tseng, A. S. & Beane, W. S. 2017 Methylisothiazolinone toxicity and inhibition of wound healing and regeneration in planaria. *Aquatic Toxicology* **191**, 226–235. <http://doi.org/10.1016/j.aquatox.2017.08.013>.
- Van Vliet, M. T. H., Jones, E. R., Flörke, M., Franssen, W. H. P., Hanasaki, N., Wada, Y. & Yearsley, J. R. 2021 Global water scarcity including surface water quality and expansions of clean water technologies. *Environmental Research Letters* **16** (2), 024020. <https://doi.org/10.1088/1748-9326/abbfc3>.
- Walls, R. M., Hockberger, R. S. & Gausche-Hill, M. 2018 *Rosen's Emergency Medicine: Concepts and Clinical Practice*. Elsevier, Philadelphia, PA, USA.
- Wang, J., Ma, M., Yang, J., Chen, L., Yu, P., Wang, J., Gong, D., Deng, S., Wen, X. & Zeng, Z. 2018 In vitro antibacterial activity and mechanism of monocaprylin against *Escherichia coli* and *Staphylococcus aureus*. *Journal of Food Protection* **81** (12), 1988–1996. <https://doi.org/10.4315/0362-028X.JFP-18-248>.
- Wang, Y., Chen, M., Wang, C., Meng, X., Zhang, W., Chen, Z. & Crittenden, J. 2019 Electrochemical degradation of methylisothiazolinone by using Ti/sno2-sb2o3/ α , β -pbo2 electrode: kinetics, energy efficiency, oxidation mechanism and degradation pathway. *Chemical Engineering Journal* **374**, 626–636. <https://doi.org/10.1016/j.cej.2019.05.217>.
- Wang, X. X., Wang, W. L., Dao, G. H., Xu, Z. B., Zhang, T. Y., Wu, Y. H. & Hu, H. Y. 2020 Mechanism and kinetics of methylisothiazolinone removal by cultivation of *Scenedesmus* sp. LX1. *Journal of Hazardous Materials* **386**, 121959. <https://doi.org/10.1016/j.jhazmat.2019.121959>.
- Warth, A. D. 1991 Effect of benzoic acid on glycolytic metabolite levels and intracellular pH in *Saccharomyces cerevisiae*. *Applied and Environmental Microbiology* **57** (12), 3415–3417. <https://doi.org/10.1128/AEM.57.12.3415-3417.1991>.
- Waters, C. M. & Bassler, B. L. 2005 Quorum sensing: cell-to-cell communication in bacteria. *Annual Review of Cell and Developmental Biology* **21**, 319–346. <https://doi.org/10.1146/annurev.cellbio.21.012704.131001>.
- Wei, D. F., Ma, Q. X., Guan, Y., Hu, F. Z., Zheng, A. N., Zhang, X., Teng, Z. & Jiang, H. 2009 Structural characterization and antibacterial activity of oligoguanidine (polyhexamethylene guanidine hydrochloride). *Materials Science & Engineering C-Materials For Biological Applications* **29** (6), 1776–1780. <https://doi.org/10.1016/j.msec.2009.02.005>.
- Wei, X., Wang, Z., Wang, J. & Wang, S. 2012 A novel method of surface modification to polysulfone ultrafiltration membrane by preadsorption of citric acid or sodium bisulfite. *Membrane Water Treatment* **3** (1), 35–49. <http://doi.org/10.12989/mwt.2012.3.1.035>.
- Weyl, O., Kaiser, H. & Hecht, T. 1996 On the efficacy and mode of action of 2-phenoxyethanol as an anaesthetic for goldfish, *Carassius auratus* (L.), at different temperatures and concentrations. *Aquaculture Research* **27** (10), 757–764. <https://doi.org/10.1046/j.1365-2109.1996.t01-1-00791.x>.
- Willi, R., Pfab, F., Zilker, T., Buters, J. & Schallock, P. 2011 Danger from the workplace: allergic contact dermatitis from the first exposure to isothiazolinones. *Contact Dermatitis* **64** (6), 361–362. <https://doi.org/10.1111/j.1600-0536.2011.01905.x>.
- Williams, T. M. 2006 The mechanism of action of isothiazolone biocide. In: *Proceedings of the 2006 NACE Corrosion Conference*, March 2006, San Diego, CA, USA.
- Williams, T. M. 2007 Methylisothiazolone: A new biocide product for closed loop systems. In: *Proceedings of the 2007 NACE Corrosion Conference*, March 2007, Nashville, TN, USA.
- Williams, T. M. & McGinley, H. R. 2010 Deactivation of industrial water treatment biocides. In: *Proceedings of the 2010 NACE Corrosion Conference*, March 2010, San Antonio, TX, USA.
- Wolf, P. A. & Sterner, P. W. 1972 2, 2-Dibromo-3-nitropropionamide, a compound with slimicidal activity. *Applied Microbiology* **24** (4), 581–584. <https://doi.org/10.1128/am.24.4.581-584.1972>.
- Woodcock, N. H., Hammond, B. H., Ralyea, R. D. & Boor, K. J. 2009 Short communication: N alpha-lauroyl-L-arginine ethylester monohydrochloride reduces bacterial growth in pasteurized milk. *Journal of Dairy Science* **92** (9), 4207–4210. <https://doi.org/10.3168/jds.2009-2150>.
- World Health Organization (WHO) 2000 *Benzoic Acid and Sodium Benzoate*. WHO, Concise International Chemical Assessment Document 26. Geneva, Switzerland. Available from: <https://apps.who.int/iris/handle/10665/42310> (accessed 27 August 2021).
- World Health Organization (WHO) 2017 *Guidelines for Drinking-Water Quality: Fourth Edition Incorporating the First Addendum*. Licence: CC BY-NC-SA 3.0 IGO. ISBN: 978-92-4-154995-0. Geneva, Switzerland. Available from: <https://apps.who.int/iris/rest/bitstreams/1080656/retrieve> (accessed 10 August 2021).
- Wu, X., Santos, R. R. & Fink-Gremmels, J. 2015 Analyzing the antibacterial effects of food ingredients: model experiments with allicin and garlic extracts on biofilm formation and viability of *Staphylococcus epidermidis*. *Food Science & Nutrition* **3** (2), 158–168. <https://doi.org/10.1002/fsn3.199>.
- Ye, S., Wei, D., Xu, X., Guan, Y. & Zheng, A. 2020 Surface antimicrobial modification of polyamide by poly(hexamethylene guanidine) hydrochloride. *Polymers for Advanced Technologies* **31** (8), 1847–1856. <https://doi.org/10.1002/pat.4911>.
- Yucel, A., Ozylacın, S., Talu, G. K., Yucel, E. C. & Erdine, S. 1999 Intravenous administration of caffeine sodium benzoate for postural puncture headache. *Regional Anesthesia and Pain Medicine* **24** (1), 51–54. [https://doi.org/10.1016/S1098-7339\(99\)90165-7](https://doi.org/10.1016/S1098-7339(99)90165-7).
- Zeng, D., Liang, K., Guo, F., Wu, Y. & Wu, G. 2020 Denitrification performance and microbial community under salinity and MIT stresses for reverse osmosis concentrate treatment. *Separation and Purification Technology* **242**, 116799. <https://doi.org/10.1016/j.seppur.2020.116799>.

- Zhang, K., Choi, H., Dionysiou, D. D., Sorial, G. A. & Oerther, D. B. 2006 Identifying pioneer bacterial species responsible for biofouling membrane bioreactors. *Environmental Microbiology* **8** (3), 433–440. doi:10.1111/j.1462-2920.2005.00909.x.
- Zhao, S., Liao, Z., Fane, A., Li, J., Tang, C., Zheng, C., Lin, J. & Kong, L. 2021 Engineering antifouling reverse osmosis membranes: a review. *Desalination* **499**, 114857. <https://doi.org/10.1016/j.desal.2020.114857>.
- Zheng, X., Zhao, Y., Jia, Y., Shao, D., Zhang, F., Sun, M., Dawulieti, J., Hu, H., Cui, L., Pan, Y., Yang, C., Sun, W., Zhang, S., He, K., Li, J., Du, J., Zhang, M. & Chen, L. 2021 Biomimetic co-assembled nanodrug of doxorubicin and berberine suppresses chemotherapy-exacerbated breast cancer metastasis. *Biomaterials* **271**, 120716. <https://doi.org/10.1016/j.biomaterials.2021.120716>.

First received 7 September 2021; accepted in revised form 5 January 2022. Available online 22 January 2022