

Hazard/Risk Assessment

Ecological Risk Analysis for Benzalkonium Chloride, Benzethonium Chloride, and Chloroxylenol in US Disinfecting and Sanitizing Products

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Abstract: Use of three topical antiseptic compounds—benzalkonium chloride (BAC), benzethonium chloride (BZT), and chloroxylenol (PCMX)—has recently increased because of the phaseout of other antimicrobial ingredients (such as triclosan) in soaps and other disinfecting and sanitizing products. Further, use of sanitizing products in general increased during the coronavirus (COVID-19) pandemic. We assessed the environmental safety of BAC, BZT, and PCMX based on best available environmental fate and effects data from the scientific literature and privately held sources. The ecological exposure assessment focused on aquatic systems receiving effluent from wastewater-treatment plants (WWTPs) and terrestrial systems receiving land-applied WWTP biosolids. Recent exposure levels were characterized based on environmental monitoring data supplemented by modeling, while future exposures were modeled based on a hypothetical triclosan replacement scenario. Hazard profiles were developed based on acute and chronic studies examining toxicity to aquatic life (fish, invertebrates, algae, vascular plants) and terrestrial endpoints (plants, soil invertebrates, and microbial functions related to soil fertility). Risks to higher trophic levels were not assessed because these compounds are not appreciably bioaccumulative. The risk analysis indicated that neither BZT nor PCMX in any exposure media is likely to cause adverse ecological effects under the exposure scenarios assessed in the present study. Under these scenarios, total BAC exposures are at least three times less than estimated effect thresholds, while margins of safety for freely dissolved BAC are estimated to be greater than an order of magnitude. Because the modeling did not specifically account for COVID-19 pandemic-related usage, further environmental monitoring is anticipated to understand potential changes in environmental exposures as a result of increased antiseptic use. The analysis presented provides a framework to interpret future antiseptic monitoring results, including monitoring parameters and modeling approaches to address bioavailability of the chemicals of interest. *Environ Toxicol Chem* 2022;41:3095–3115. © 2022 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

Keywords: Quaternary ammonium compounds; surfactants; antimicrobials; contaminants of emerging concern; environmental modeling; NICA-Donnan model

INTRODUCTION

In recent years, chemicals used in topical antiseptic applications—most notably triclosan and triclocarban—have faced public scrutiny because of concerns about their effects on the environment when used in products that are rinsed down household and commercial drains. Major manufacturers began removing triclosan from topical antiseptics and other products in 2011, and formal bans in the United States took effect for consumer hand washes manufactured after 2017 and

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Published online 11 September 2022 xxxx in Wiley Online Library

(wileyonlinelibrary.com).

DOI: 10.1002/etc.5484

health care hand washes and rubs manufactured after 2018 (Food and Drug Administration, 2016a, 2017). Because triclosan and triclocarban have been phased out of soaps and other products, attention on environmental effects has shifted to their replacements, benzalkonium chloride (BAC), benzethonium chloride (BZT), and chloroxylonol (also known as parachlorometaxylenol or PCMX). Use of these and other sanitizing agents increased further during the COVID-19 pandemic (Hora et al., 2020; Zheng et al., 2020), although such applications may have peaked because medical advice has focused increasingly on guarding against airborne rather than surface-mediated transmission. It is too early to quantify how increased use of such products affected the amounts of BAC, BZT, and PCMX going down the drain and entering wastewater-treatment systems (i.e., Zheng et al. [2020] found increased concentrations specifically in household dust rather than in water).

Benzalkonium chloride is a group of quaternary ammonium salts neutralized by chloride, with a nitrogen cation bonded to a benzyl group, two methyl groups, and an alkyl chain, which can range in length from 8 to 18 carbons (e.g., BAC-C8 has eight carbons). The chloride counterion dissociates on dissolution in water. The data compiled for this paper show that BAC-C12 and BAC-C14 are the most prevalent BAC compounds in wastewater influent. Benzalkonium chloride is a cationic surfactant with increased sorption at longer alkyl chain lengths (García et al., 2006) and is highly soluble in water ($S_w = 10\text{--}750$ g/L depending on alkyl chain length), is soluble in alcohol, and has a median vapor pressure (V_p) of 7.5×10^{-9} Pa (European Chemicals Agency [ECHA], 2013; Ismail et al., 2010; US Environmental Protection Agency [USEPA], 2019a). It is readily biodegradable (European Chemicals Agency, 2013; García et al., 2001). As a class, cationic surfactants generally exhibit low bioaccumulation potential, tending to be retained on epithelial surfaces rather than crossing cell membranes (National Industrial Chemicals Notification and Assessment Scheme [NICNAS], 2016). Consistent with this pattern, experimental bioconcentration factors for BAC in fish are <100 (Krzeminski et al., 1977; NICNAS, 2016; Standing Committee on Biocidal Products, 2012), whereas compounds are classified as *bioaccumulative* based on bioconcentration factors >1000 under the USEPA's Toxic Substances Control Act (TSCA) program. Kaj et al. (2014) measured quaternary ammonium compounds in fish collected from several Nordic countries; as expected, detection frequencies and concentrations were low. Specifically, BAC-C12 was never detected, whereas BAC-C14, -C16, and -C18 were detected in 5%, 47%, and 26% of fillet samples, respectively; and detectable BAC concentrations were <5 $\mu\text{g}/\text{kg}$ in all fillet samples. The shift in predominant BAC compounds from BAC-C12 and -C14 in wastewater to BAC-C16 and -C18 in fish tissue is most likely due to differences in relative bioaccumulation potential, which—while remaining low relative to hydrophobic organic contaminants—is expected to increase with alkyl chain length. Benzalkonium chloride is a widely used biocide in industrial, commercial, medical, agricultural, food handling, and residential settings

and targets bacteria, fungi, viruses, and algae (USEPA, 2006). Additional diverse industrial and commercial uses take advantage of BAC's surfactant (rather than biocidal) properties.

Benzethonium chloride is another quaternary ammonium salt and cationic surfactant comprising two phenyl groups (one with an attached trimethylpentane) linked by a chain with a quaternary nitrogen and two ether functionalities. It is very soluble in water ($S_w = 10$ to >530 g/L) and soluble in alcohol (ECHA, 2017; Li, 2008; National Institutes of Health [NIH], 2019). The median estimate of V_p is 1.4×10^{-8} Pa (ECHA, 2017; USEPA, 2019a), and BZT is not readily biodegradable (ECHA, 2017). The bioaccumulation potential of BZT has not been studied but is inferred to be low based on general observations for cationic surfactants, described above for BAC. Less widely used than BAC, BZT is an ingredient in skin disinfectants, cosmetics, and toiletries and can be used against bacteria, fungi, mold, and viruses (NIH, 2019).

Chloroxylonol is a xylonol with chlorine substituted into the benzene ring. It is polar and only moderately hydrophobic, with a log octanol–water partition coefficient (K_{OW}) of 3.3 (USEPA, 2019a). It is more volatile (median $V_p = 0.24$ Pa) and less soluble (median $S_w = 0.3$ g/L) than BAC and BZT (Faludi et al., 2015; Kim et al., 2016; USEPA, 2019a; Yalkowsky & He, 2003). It is biodegradable (see section *PCMX exposure assessment* for details). Although PCMX bioaccumulation has not been measured, aquatic bioaccumulation of a variety of similar chlorinated phenols has been determined, such that estimation of bioconcentration factors based on K_{OW} is well supported. Fish bioconcentration factors of 30–70 are estimated (Saarikoski & Viluksela, 1982; USEPA, 2019a), indicating that PCMX is not bioaccumulative. It has long been used as a topical antiseptic that targets bacteria, algae, and fungi by denaturing proteins and inactivating enzymes. It is also used for industrial purposes, such as in adhesives and latex paints (USEPA, 1994).

In the present study we evaluate the ecological risks posed by BAC, BZT, and PCMX as used in disinfecting and sanitizing products such as antiseptic hand washes, disinfecting laundry detergents, and health care antiseptics. The analysis focuses primarily on environmental exposures in the United States, but we also supplement US data with international data as needed to address limitations in US monitoring data. Estimating current usage is difficult because it is continuously changing, which is due to product reformulations and evolving consumer disinfection and sanitizing practices. To address this issue, we consider two use scenarios: a recent past scenario, characterized primarily based on environmental monitoring data, and a hypothetical future scenario, informed by the recent past scenario and assuming replacement of triclosan (as measured in wastewater-treatment plant [WWTP] influent [Bock et al., 2010]) by each of the three target compounds. Although the triclosan replacement scenario is plausible, the extent to which it resembles pandemic-related usage for each target compound is uncertain, and future monitoring is expected to address this knowledge gap (Hora et al., 2020). In addition to forecasting potential future exposures under the assumed conditions, the future scenario serves to demonstrate methods

to quantify environmental fate and bioavailability of the subject compounds. Such methods are well established for nonionizing organic chemicals such as PCMX but are novel for cationic surfactants such as BAC and BZT. The risk analysis framework developed in the present study may also be adapted for other surfactants and product ingredients that reach the environment through down-the-drain pathways.

METHODS

Conceptual model of exposure

The present assessment focuses on environmental exposures for the target compounds stemming from their use in disinfecting/sanitizing products; specific uses, such as hand washes versus floor cleaners, are not distinguished. The target compounds BAC, BZT, and PCMX are transferred to WWTPs as influent by way of down-the-drain disposal. Much of the initial loading to WWTPs is degraded or partitions to sludge. The sludge, in turn, may be disposed or may be treated for beneficial use as a soil amendment (termed *biosolids*). Fractions of the target compounds not degraded during treatment can enter the environment in discharged effluent and land-applied biosolids (DeLeo et al., 2020).

After discharge, WWTP effluent mixes with surface water, and the target compounds establish an equilibrium between surface water and sediment. Aquatic organisms, such as fish, macroinvertebrates, and aquatic plants, can be exposed to the target compounds in these media. Land-applied biosolids are mixed with soil, where plants, invertebrates, and the soil microbial community can be exposed. Biosolids are most often applied to agricultural fields but are also applied to non-agricultural lands (e.g., for land reclamation). Based on this conceptual model, relevant environmental exposure media are surface water, sediment, and soil. Bioaccumulation in the food web is not a relevant ecological exposure pathway because BAC, BZT, and PCMX all have low bioaccumulation potential.

Data compilation

Data to support this environmental risk assessment were compiled through a thorough literature search and by soliciting proprietary data from American Cleaning Institute member companies. Publicly available data were identified using Scopus and Google Scholar search engines and by searching multiple government databases. The literature search strategy is further detailed in Supporting Information, 1.

Data sources were reviewed for appropriate study design, documentation, and data quality. Consistent with USEPA (2003a) guidance, data quality assessment factors included soundness (i.e., the extent to which the study design and methods are appropriate to the researchers' intended application), applicability and utility (i.e., the extent to which the study is appropriate to our intended application), clarity and completeness, appropriate consideration of uncertainty and variability (e.g., through statistical analysis), and evaluation and review by others. We independently evaluated the data quality of peer-reviewed

publications and other reports. A substantial amount of additional data was available only from variously detailed summaries of proprietary data sources, which we evaluated as follows. For data available only from Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers, we relied on the reported reliability score as well as our review of the study details provided. The dossiers for BAC, BZT, and PCMX have each received a comprehensive review by the ECHA. Data from the Japan Chemicals Collaborative Knowledge database were reviewed in a manner analogous to the REACH dossiers. For data obtained from USEPA's Office of Pesticide Programs Pesticide Ecotoxicity Database, which primarily contains "unpublished data that has been carefully reviewed by [USEPA]" (USEPA, 2019b), we relied on USEPA's prior data quality review.

Exposure assessment

The objective of the exposure assessment is to estimate exposure concentrations in environmental media (i.e., surface water, sediment, soil), in both the recent past and future scenarios. Figure 1 identifies which components of the exposure analysis were based on monitoring versus modeling for each chemical and scenario. For most media and scenarios, we developed both central-tendency and high-end exposure estimates, resulting in up to four exposure estimates for each target compound in surface water, sediment, and soil. Appropriate monitoring data were used preferentially to characterize exposures for the recent past scenarios, if available; data gaps were addressed through modeling. The future scenario relied primarily on modeling, based on replacement usage following the phaseout of triclosan and triclocarban. The complete replacement of triclosan and triclocarban by BAC, BZT, or PCMX is a conservative (i.e., protective) assumption because it is far more likely that triclosan and triclocarban will be replaced by some combination of these compounds, as well as others not assessed in the present study (e.g., alcohols). The present analysis provides a framework that will aid interpretation of future environmental monitoring data for the antiseptic compounds of interest.

Monitoring data. Environmental monitoring data for BAC, BZT, and PCMX were compiled for matrices that either represent ecological exposure media or can be used to estimate concentrations in ecological exposure media. Thus, measured concentrations of the target compounds were compiled for surface water, sediment, wastewater influent, wastewater effluent, and digested sludge or biosolids (from wastewater treatment). We also searched for reported concentrations of target compounds in soil that received land-applied biosolids, but these were almost entirely lacking, aside from a single sample result (Heyde et al., 2020). Non-US surface water data were excluded if they were confirmed to be from water bodies receiving untreated sewage. In such situations, other stressors such as pathogens and biological oxygen demand are much more environmentally significant than possible effects related to antimicrobials in the sewage (see Eisenberg et al., 2016). Thus, although raw sewage releases do occur in the

Compound	Scenario	WWTP loading		Removal efficiency	Biosolids	Surface water EPCs	Sediment EPCs	Soil EPC(s)
BAC	Recent past	— ^a		—	Median and high end	Median and high end	Median and high end	Modeled from biosolids (median and high end)
	Projected future	Baseline (median and high end)	Triclosan replacement (point estimate)	Median	Modeled from WWTP loading	Modeled distribution (median and high end)	Modeled from surface water	Modeled from biosolids (median and high end)
BZT	Recent past	--		—	Median and high end	Qualitative: infer from non-detected effluent data	Median and high end	Modeled from biosolids (median and high end)
	Projected future	Triclosan replacement (point estimate)		Modeled point estimate	Modeled from WWTP loading	Modeled distribution (median and high end)	Modeled from surface water	Modeled from biosolids (point estimate)
PCMX	Recent past	Median and high end		—	Modeled from WWTP loading	Median and high end	Modeled from surface water	Modeled from biosolids (median and high end)
	Projected future	Triclosan replacement (point estimate)		Median	Modeled from WWTP loading	Modeled distribution (median and high end)	Modeled from surface water	Modeled from biosolids (point estimate)

FIGURE 1: Basis for key elements of environmental exposure scenarios, including mass loading to wastewater-treatment plants (WWTP), percentage of removal from wastewater during treatment, WWTP biosolids concentrations, and exposure point concentrations. Monitoring data were used for recent past scenarios if available, with data gaps addressed through modeling. Colors represent values obtained via monitoring data (blue), modeling (pink), or assumption (light green). EPC = exposure point concentration; BAC = benzalkonium chloride; BZT = benzethonium chloride; PCMX = chloroxylenol.

United States, sewage management upgrades are the appropriate way to address this problem, regardless of any ingredients in cleaning products (Botturi et al., 2021; USEPA, 2004). In the environmental monitoring database, total BAC concentrations and WWTP removal efficiencies for target compounds were used as reported by the original references where available. Otherwise, concentrations of individual BAC compounds for each sample were summed using one-half of the detection limit for nondetect results, and removal efficiencies were calculated from paired influent and effluent data (see Supporting Information, 2, for details).

The US monitoring data are sufficient to fully support exposure characterization only for PCMX in surface water (see section *PCMX exposure assessment*). For BAC and BZT, the available US data were either too sparse (surface water) or too geographically limited (sediment) to adequately characterize US exposures; therefore, data were compiled from studies conducted in the United States and in northern and western Europe. Global data are included in the removal efficiency evaluation for all target compounds.

Where WWTP loadings or environmental exposure concentrations were derived from monitoring data, central-tendency exposure estimates were based on medians, and high-end exposure estimates were based on the 95th percentiles of the

applicable data sets. However, only the median estimate was applied for removal efficiencies, to avoid unrealistic scenarios resulting from compounding conservative assumptions for multiple model inputs. The resulting exposure point concentrations are conservative (i.e., protective) with respect to environmental releases related to disinfecting/sanitizing products because environmental monitoring data reflect the totality of uses of the target compounds. In particular, uses of BAC are diverse, and observed concentrations may reflect environmental sources such as agricultural applications, in addition to sources related to consumer use of disinfecting/sanitizing products.

Exposure modeling. Figure 2 illustrates the exposure modeling framework applied in this assessment for the future scenario and to fill data gaps in the recent past scenario. Environmental fate and transport modeling considered inputs of BAC, BZT, and PCMX to municipal wastewater-treatment systems; degradation during wastewater treatment; partitioning to biosolids during wastewater treatment; dilution of treated effluent through mixing with environmental media in the mixing zone; degradation after release to surface water; partitioning between surface water and sediments on release to aquatic environments; partitioning between freely dissolved and complexed states in surface water; and dilution of biosolids

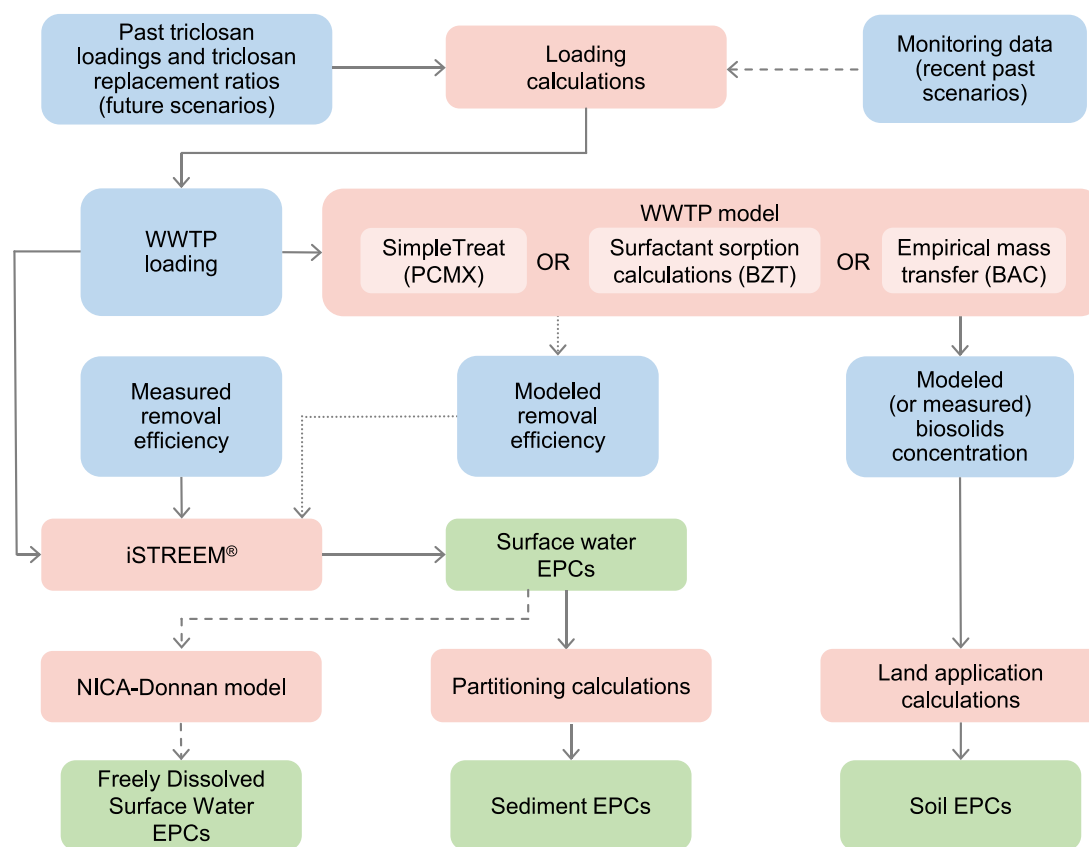


FIGURE 2: Conceptual approach to exposure modeling, used for the future scenario and to fill data gaps for the recent past scenario. Dashed line = modeling components applicable only to benzalkonium chloride (BAC); dotted line = modeling components applicable only to benzethonium chloride (BZT). Colors represent inputs and intermediate values (blue), calculations (pink), and outputs (green). WWTP = wastewater-treatment plant; PCMX = chloroxynol; EPC = exposure point concentration; NICA = nonideal competitive adsorption.

via land application. An overview of the models and model components used in the present analysis is provided below, with additional details provided in Tables 1–3 and Supporting Information, 3.

Loadings. Estimates of target compound loading to WWTPs were required to support modeling for the future scenario, as well as to address data gaps for the PCMX recent past scenario (Figure 1). For the recent past scenario, median and 95th percentile concentrations from WWTP influent monitoring data were converted to per capita mass loadings based on a per capita wastewater volume of 400 L/day (Struijs, 2014). The future scenario considered hypothetical estimates of the substitution of BAC, BZT, or PCMX for formerly used antimicrobials, as represented by triclosan. Because triclosan and the replacement compounds are used in different concentrations to achieve an equivalent antiseptic effect, replacement ratios were empirically estimated based on concentrations used in similar products. Loadings for the future scenario were estimated as

$$L = [A + (B \times C)] \times D \quad (1)$$

where L is loading (micrograms per person per day), A is the baseline concentration of the target compounds in WWTP influent prior to triclosan replacement (micrograms per liter); B is

the triclosan concentration to be replaced, based on a selected percentile from a distribution of triclosan concentrations in WWTP influent (micrograms per liter; Bock et al., 2010); C is the triclosan replacement ratio (unitless); and D is the per capita daily wastewater volume (liters per person per day). The future loading estimates for BAC and PCMX are based on a median triclosan influent concentration, whereas the future BZT loading estimate is based on the lower quartile of the triclosan data distribution because BZT is used much less widely than the other two target compounds. This approach approximates usage changes, given that, on the one hand, the target compounds are actually replacing more antimicrobial compounds than just triclosan, while, on the other hand, triclosan is actually being replaced by multiple replacement compounds rather than one compound at a time, and not all former triclosan uses are being replaced with BAC, BZT, or PCMX (e.g., former use of triclosan in toothpaste).

The baseline component of future loading was negligible compared to the triclosan replacement component for BZT and PCMX. For BAC, median and high-end baseline loadings were identified from influent monitoring data. However, the high-end baseline estimate was only used to estimate future soil BAC concentrations. Future aquatic exposures were estimated using a model that generates a conservative distribution of surface water concentrations (see *Mechanistic WWTP*

TABLE 1: Chemical-specific exposure model inputs for benzalkonium chloride

Model	Parameter	Units	Value	Basis
Loading	BAC influent concentration (recent past scenario and baseline for future scenario)	µg/L	17–105	Median and 95th percentile from monitoring data (present study)
	Triclosan concentration to be replaced	µg/L	4.8	Median in WWTP influent (Bock et al., 2010)
	Triclosan replacement ratio	Unitless	1.7	Ratio of midpoint concentrations of BAC versus triclosan in consumer hand wash products (Food and Drug Administration, 2016b)
iSTREEM	Primary only	% Removal	50	BAC-C12 and BAC-C14 empirical mass transfer to primary sludge (Östman et al., 2018)
	Standard (activated sludge)	% Removal	99.0	Median of average BAC-C12 and BAC-C14 removal efficiencies (present study)
	Tricking filter/rotating biological contactor	% Removal	97.4	Median of average BAC-C12 and BAC-C14 removal efficiencies (present study)
	Instream decay constant	Day ⁻¹	0.324	First-order rate constant for removal, calculated ^a from Environmental Control Center (2017). Average of BAC-C12 and BAC-C14 rates
WWTP empirical mass transfer	Mass transfer to sludge	%	56	Average of mass transfer coefficients for BAC-C12 and BAC-C14 from Bromma and Rya WWTPs (Östman et al., 2018)
	Digested sludge production rate	g dry wt/L influent	0.124	Average digested sludge production values for three WWTPs (Östman et al., 2018)
	Partition coefficient (K _d)	L/kg dry wt	55 324	Weighted average K _d value calculated using K _d values for BAC-C12 (20,249), -C14 (45,143), -C16 (100,856), and -C18 (225,893) and median contributions of BAC-C12 (58%), -C14 (24%), -C16 (7%), and -C18 (12%) to the total detected BAC in effluent and surface water
Biosolids land application	Recent past biosolids concentrations	mg/kg	46–118	Median and high-end estimates from monitoring data (present study)
	Projected future biosolids concentrations	mg/kg	114–513	Median and high-end estimates from empirical WWTP model (present study)

^aCalculated using first-order integrated rate law.

BAC = benzalkonium chloride; WWTP = wastewater-treatment plant.

TABLE 2: Chemical-specific exposure model inputs for benzethonium chloride

Model	Parameter	Units	Value	Basis
Loading	Triclosan concentration to be replaced	µg/L	3.1	Lower quartile in WWTP influent (Bock et al., 2010)
	Triclosan replacement ratio	Unitless	1.0	Assumption, informed by anecdotal information
iSTREEM	Primary only	% Removal	66.7	Mechanistic WWTP model (present study)
	Standard (activated sludge)	% Removal	99.9	Mechanistic WWTP model (present study)
	Tricking filter/rotating biological contactor	% Removal	97.4	Measured percentage removal for BAC (present study) as a conservative surrogate
	WWTP biodegradation classification	NA	Not biodegradable ^a	European Chemicals Agency (2017)
Mechanistic WWTP	WWTP biodegradation rate constant	h ⁻¹	0.0	European Commission (2003)
	CMC	g/L	1.33	Median of experimentally derived values (Kopecký et al., 2007; Oremusová et al., 2012)
Soil partitioning	Adsorption capacity factor (K)–primary and waste-activated sludge	(mg/g VS)/(L/mg)	10.6	Calculated using relationship between CMC and K presented in Ismail et al. (2010) (log K = 0.6 – 0.9 x log CMC)
	Intensity parameter (1/n)–primary and waste-activated sludge	Unitless	0.38	Calculated using relationship between K and 1/n presented in Abe et al. (1982) (1/n = 0.186 x log K + 0.572); K above used as input
Sediment partitioning	Partition coefficient (K _d)	L/kg dry wt	12 541	K _d value calculated using cation-exchange sorption model (Droge & Goss, 2013c)
	Partition coefficient (K _d)	L/kg dry wt	37 978	K _d value calculated using cation-exchange sorption model (Droge & Goss, 2013c)
Biosolids land application	Recent past biosolids concentrations	mg/kg	0.034–0.079	Median and high-end estimates from monitoring data (present study)
	Projected future biosolids concentrations	mg/kg	10.7	Mechanistic WWTP model (present study)

^aNo carbon dioxide evolution in 28-day incubation.

WWTP = wastewater-treatment plant; NA = not applicable; CMC = critical micelle concentration; VS = volatile solids.

TABLE 3: Chemical-specific exposure model inputs for chloroxylenol

Model	Parameter	Units	Value	Basis
Loading	PCMX influent concentration (recent past scenario)	µg/L	0.22–0.84	Median and 95th percentile, calculated from effluent monitoring data and percentage removal for activated sludge WWTPs (present study)
	Triclosan concentration to be replaced Triclosan replacement ratio	µg/L Unitless	4.8 3.0	Median in WWTP influent (Bock et al., 2010) Assumption. Usage ratios for PCMX versus triclosan are 1.7 for consumer products (large market) and 10 for health care products (smaller market), based on data from Food and Drug Administration (2015, 2016b)
iSTREEM	Primary only Standard (activated sludge)	% Removal % Removal	3.4 91.5	Mechanistic WWTP model (present study) Median of PCMX removal efficiencies (Kasprzyk-Hordern et al., 2009; Oppenheimer et al., 2007; Yu et al., 2012)
	Tricking filter/rotating biological contactor K _{OC} Water solubility	% Removal L/kg mg/L	90.1 800 300	Kasprzyk-Hordern et al. (2009) Median of MCI and K _{OW} estimates (EpiSuite 4.1) Median estimated and experimental values (EpiSuite 4.1; Faludi et al., 2015; Yalkowsky & He, 2003)
Mechanistic WWTP (SimpleTreat 4.0)	Henry's law coefficient	Pa/m ³ /mol ¹	0.065	Median estimates (EpiSuite 4.1)
	Vapor pressure	Pa	0.24	Modified grain method estimate (EpiSuite 4.1)
	Molecular weight	g/mol	156.6	EpiSuite 4.1
	WWTP biodegradation classification	NA	Inherently biodegradable ^a	European Chemicals Agency (2018); multiple studies reported differing biodegradability estimates (see text)
Sediment partitioning Biosolids land application	WWTP biodegradation rate constant	h ⁻¹	0.1	European Commission (2003)
	K _{OC}	L/kg	800	Median of MCI and K _{OW} estimates (EpiSuite 4.1)
	Recent past biosolids concentrations	mg/kg	0.039–0.15	Median and high-end estimates from mechanistic WWTP model (present study)
	Projected future biosolids concentrations	mg/kg	2.6	Median estimate from mechanistic WWTP model (present study)

^aNot readily biodegradable but degradation demonstrated using realistic exposure conditions (higher microbial biomass, semicontinuous activated sludge reactor, etc.).
PCMX = chloroxylenol; WWTP = wastewater-treatment plant; K_{OC} = organic-carbon partition coefficient; MCI = molecular connectivity index; K_{OW} = octanol-water partition coefficient; EpiSuite = Estimation Programs Interface Suite; NA = not applicable.

modeling). Therefore, only the median loading rate was used to model future aquatic exposures for BAC, to avoid compounding conservative assumptions.

For PCMX in the recent past scenario, terms *B* and *C* were removed from the loading calculation. That is, the loading was simply back-calculated from the estimates of influent concentration and wastewater volume.

Modeled concentrations in surface water. Concentrations of the target compounds in surface water were modeled from estimated loadings using iSTREEM[®] (Kapo et al., 2016). This model incorporates detailed, spatially explicit information on WWTP and receiving water characteristics throughout the United States to yield estimated concentrations of “down-the-drain” chemicals in effluent and receiving waters. The model generates a distribution of predicted surface water concentrations throughout the United States based on annual mean flow or low-flow conditions (lowest 7-day average flow that occurs once every 10 years) in receiving waters. For risk-characterization purposes, we consider both the full output distributions and selected exposure point concentrations from the low-flow distribution (i.e., medians and 95th percentiles of model output).

The iSTREEM model uses removal efficiency from wastewater as an input, which we parameterized based primarily on monitoring data for BAC and PCMX and using a mechanistic WWTP model for BZT. The iSTREEM model requires removal efficiencies specific to multiple WWTP types; parameterization is described in Supporting Information, 3. Notably, iSTREEM allows for a chemical-specific loss constant to account for in-river biodegradation, sedimentation, and other loss mechanisms from surface water. This input was parameterized for BAC based on a study of biodegradation in river water with no sediment (Environmental Control Center, 2017), thus neglecting in-river sorption to sediment due to insufficient data to parameterize this important loss mechanism from surface water. In-river loss could not be incorporated at all in the model for PCMX and BZT because of a lack of applicable environmental fate data. Kapo et al. (2016) compared iSTREEM-modeled concentrations to monitoring data for two well-characterized compounds and found that the model tended to overestimate the higher end of the concentration distribution, especially under low-flow conditions. For the present analysis, the in-river loss assumptions are highly conservative for all three target compounds, and thus the iSTREEM model predictions are likely to be even more conservative than those reviewed by Kapo et al. (2016). The surface water monitoring data for BAC and PCMX also shed light on model conservatism and realism (see *Results*).

Aqueous bioavailability modeling. For quaternary ammonium compounds such as BAC and BZT, reduction of aqueous bioavailability through sorption and complexation is pronounced (DeLeo et al., 2020; Nabholz et al., 1993; NICNAS, 2016). In the present study, we used the nonideal competitive adsorption (NICA)–Donnan model of ion complexation with humic material (Milne et al., 2003) to determine concentrations of freely dissolved (i.e., bioavailable) BAC, which more accurately characterize bioavailable exposures and toxic potential in laboratory

and environmental conditions, compared with total BAC (Ishiguro & Koopal, 2016; Milne et al., 2003). Humic substances are high-molecular weight organic compounds that carry a negative charge and readily bind cations (Reuter & Perdue, 1977). Previously NICA–Donnan models have been used to describe the binding of quaternary ammonium compounds to humic material (Chen et al., 2013; Ishiguro & Koopal, 2011).

The NICA–Donnan model couples a NICA model with a Donnan electrostatic model to describe how ions interact with humic material. The Donnan electrostatic model assumes that the negatively charged groups in humic material generate an electric field in the aqueous phase around the material (the Donnan phase). Cations are attracted to and accumulate in the Donnan phase to maintain electroneutrality. The NICA model describes binding of cations to the specific charged sites of the humic material. An advantage of the NICA–Donnan model is that, once the correct parameters for the model are determined, it can be applied to samples with different water compositions (e.g., different major ion concentrations). Chen et al. (2013) parameterized a NICA–Donnan model for BAC. However, because of an error discovered in the model input, we were not able to use their NICA–Donnan parameterization results. Instead, we used the data they reported for BAC binding to Sigma-Aldrich humic material to reparameterize the NICA–Donnan model, as described in Supporting Information, 3. Comparable data are not available for BZT. All NICA–Donnan modeling was run using Visual MINTEQ geochemical software (Gustafsson, 2013).

The NICA–Donnan model was applied to BAC exposure point concentrations for the recent past and future scenarios to estimate freely dissolved concentrations. Environmental inputs to the model (ionic strength and humic substance concentrations) were derived from the USEPA's National Rivers and Streams Assessment (USEPA, 2020). Interpretation of ionic strength from this data set is described in Supporting Information, 3. Because WWTP discharges are the primary source of BAC to natural waters and are characterized by high dissolved organic carbon (DOC) content, the median, 80th, and 90th percentile values of DOC from the data set were used in the model (3.42, 6.98, and 10.8 mg/L, respectively). The 90th percentile concentration agrees well with the total organic carbon (TOC) concentration used in the TSCA approach to quantifying mitigation of surfactant toxicity by humic substances (10 mg/L [Nabholz et al., 1993]). The selected DOC concentrations were applied as an approximation of the humic carbon concentration. Typically, 60%–80% of DOC in natural waters is humic (Reuter & Perdue, 1977). On the other hand, humic substances are found in both the DOC and TOC size fractions, so DOC concentrations alone underestimate the relevant organic carbon pool. In setting humic carbon equal to DOC, we implicitly assumed that these two biases cancel one another. Because carbon typically comprises 50% of the mass of humic material (Reuter & Perdue, 1977), the DOC concentration was multiplied by 2 to estimate the humic matter concentration for input into the model.

Mechanistic WWTP modeling. Mechanistic WWTP models are well developed for nonionic organic compounds such as

PCMX, but a customized approach is required to appropriately model WWTP removal for surfactants. For BAC, enough monitoring data are available to support empirical parameterization of removal from wastewater as well as transfer to biosolids (an input for estimating concentrations in soil; see section *Empirical WWTP modeling*). For BZT and PCMX, mechanistic modeling was used to estimate concentrations in biosolids and to fill data gaps for removal efficiency as an input to iSTREEM (see section *Modeled concentrations in surface water*). The mechanistic WWTP model for the present analysis included an existing model—SimpleTreat—designed for hydrophobic organic compounds (Struijs, 2014), as well as customized sorption calculations to account for concentration-dependent sorption of the surfactant BZT. SimpleTreat simulates the degradation and sorption processes that contribute to removal during wastewater treatment. The model distinguishes transfer to biosolids from removal via degradation and thus predicts target compound concentrations in both WWTP effluent and biosolids (although the resulting effluent estimates were not used in the present analysis). SimpleTreat's predictions compare well to measured data for many consumer chemicals (see Franco et al., 2013a, 2013b; Lautz et al., 2017). SimpleTreat inputs were set at model defaults except for sewage flow, which was assumed to be 400 L/day to represent US conditions.

Sorption is inherently a concentration-dependent process because sorption sites can become saturated at sufficiently high chemical concentrations. However, for nonpolar hydrophobic organic compounds like PCMX, this concentration dependence is generally considered negligible for environmental modeling purposes, and the organic carbon–water partition coefficient (K_{OC}) is treated as a constant, as in SimpleTreat. Concentration dependence is more important for surfactants because they sorb to specific binding sites via charge–charge interactions. Therefore, partitioning of BZT to biosolids was modeled using adsorption isotherm equations.

Surfactant sorption was estimated in the WWTP model using Freundlich isotherms, which take the following form:

$$\log(C_{\text{solid}}) = \log(K) + \frac{1}{n} \log(C_{\text{aqueous}}) \quad (2)$$

In Equation 2, C_{aqueous} is the equilibrium concentration in the aqueous phase, C_{solid} is the equilibrium concentration in the solid phase, and K and n are experimentally determined constants. In applying the Freundlich equation to estimate partitioning during wastewater treatment, the incoming aqueous surfactant concentration is not the same as the aqueous equilibrium concentration. In this closed system, the loss of surfactant from the aqueous phase as it sorbs to solids must be taken into account, as follows:

$$\log(C_{\text{solid}}) = \log\left(\frac{x}{y}\right) = \log(K) + \frac{1}{n} \log(C_i - x) \quad (3)$$

In Equation 3, x is the surfactant concentration lost from the aqueous phase (milligrams per liter), C_i is the incoming surfactant concentration before sorption (milligrams per liter), and

y is the solids concentration (grams per liter). For modeling purposes, volatile and total solids are treated as equivalent because the variability in solids content is greater than the difference between total and volatile solids. This equation was solved iteratively using a symbolic processor.

The WWTP modeling was implemented for BZT in a stepwise fashion, to simulate primary and secondary treatment. Sorption during primary treatment was estimated using the C_i for WWTP influent and a solids concentration of 0.225 g/L (Struijs, 2014). To estimate sorption during secondary treatment, the solids concentration was adjusted to 0.2 g/L (Clark et al., 1995; Struijs, 2014), and the C_i term was identified as the postsorption surfactant concentration in primary effluent (secondary influent). In biosolids, BZT concentrations were estimated by taking the weighted average concentration in primary sludge and secondary (i.e., wasted) sludge, based on the solids balance assumed in the SimpleTreat model. Biodegradation of BZT was assumed to be negligible (see section *BZT exposure assessment*). Details are provided in Supporting Information, 3.

Empirical WWTP modeling. An empirical WWTP model was developed with data from Östman et al. (2018) to estimate concentrations of BAC in biosolids and to fill data gaps for removal efficiency as an input to iSTREEM. Östman et al. (2018) measured concentrations of BAC during various treatment steps in three Swedish WWTPs equipped with secondary treatment. Primary treatment removal efficiency was estimated based on the mass percentage of BAC in influent transferred to primary sludge. Concentrations of BAC in biosolids were estimated using the percentage of BAC mass in influent transferred to digested sludge and the sludge production rate per unit of influent (Supporting Information, 3). Results from the Ön WWTP in Umeå were excluded from estimates of mass transfer to biosolids because this plant was found to be less efficient as a result of extreme cold; the plant is located near the Arctic Circle (i.e., unfavorable for biodegradation).

Partitioning from surface water to sediment. Partition coefficients were identified to facilitate predictions of target compound concentrations in sediment. Specifically, sediment concentrations were estimated from surface water exposure point concentrations for the future scenario, as well as for PCMX in the recent past scenario because of lack of sediment monitoring data for this compound. For PCMX, a standard equilibrium partitioning equation was applied (Di Toro et al., 1991).

$$C_{\text{solid}} = C_{\text{aqueous}} \times K_{OC} \times OC \quad (4)$$

In Equation 4, OC represents the organic carbon content of the solid media, expressed as a fraction. A typical and reasonably conservative assumption of 1% sediment organic carbon content was applied.

A sorption model for organic cations in soil developed by Droge and Goss (2013a, 2013b, 2013c) was selected as the most robust approach to estimate sediment concentrations of BAC and BZT. In contrast to the closed system simulated for sorption of these surfactants to sludge, sorption to sediment is modeled

as an equilibrium between in-place sediment and continuously renewing effluent discharge. Droge and Goss (2013a, 2013b, 2013c) developed quantitative structure–activity relationship models to predict cation sorption coefficients for clay minerals and organic carbon, which are combined to calculate an overall sorption coefficient (K_d) to soil. Although the model was derived for sorption to soil, it is equally valid for sorption to sediment given the commonality of sorbents in soils and sediments. The model allows users to define the cation-exchange capacity (CEC) and fraction organic carbon of the sediment of interest. A CEC of 20 cmol charge/kg was selected, which is representative of medium-to-fine textured calcareous till and medium-textured recent alluvium glacial till (Bergstrom et al., 1987). A typical and reasonably conservative assumption of 1% sediment organic carbon content was applied. Values of K_d were developed for BAC-C8 through -C18. To identify an overall K_d applicable to a typical BAC mixture, a weighted average log K_d of 4.74 was calculated based on median contributions of each BAC compound to the total detected BAC in effluent and surface water samples (Table 1; Supporting Information, Tables S3–S9).

In addition to the selected approach, Langmuir isotherms developed from soil experiments were considered, but their application in this context would have required extrapolating four orders of magnitude below the range of the underlying data (Khan et al., 2017). Ndabambi and Kwon (2020) also presented a method for deriving K_d values for BAC in soils; but that model was only applicable to a subset of the BAC compound of interest, and we judged the model less robust based on clarity of inputs and plausibility of results compared to other methods and observed sediment concentrations. Details of the K_d derivation for BAC and BZT are provided in Supporting Information, 3.

Land application modeling. Concentrations in soil following land application of biosolids were estimated based on the dilution of biosolids as they are mixed into soil. Biosolids were assumed to be applied at the geometric mean annual application rate (AR) of 1.9 kg/m², on a dry weight basis, with a till depth (D) of 0.2 m (Fuchsman et al., 2010). Concentrations in soil were estimated as

$$C_{\text{soil}} = \frac{C_{\text{Biosolids}} \times \text{AR}}{(D \times \rho_{\text{soil}}) + \text{AR}} \quad (5)$$

where C_{soil} is the concentration in soil (milligrams per kilogram), $C_{\text{biosolids}}$ is the concentration in biosolids (milligrams per kilogram), and ρ_{soil} is the soil density (1500 kg/m³ [Mackay, 2001]). This approach does not account for in-field biodegradation or year-over-year accumulation of target compounds in soil. In-field biodegradation likely occurs for BAC and PCMX, reducing concentrations over time, whereas BZT may not be readily degraded and could potentially build up to higher concentrations in soil after repeated biosolids applications.

Effects assessment

Toxicity data compilation. To support the effects assessment, we compiled from the peer-reviewed and gray literature acute and chronic ecotoxicity data for BAC, BZT, and PCMX

effects on aquatic and benthic invertebrates, fish, algae, and aquatic plants; terrestrial invertebrates and plants; and microbial processes relevant to soil fertility (e.g., nitrogen cycling). The types of organisms selected for inclusion reflect valued ecosystem components that are typically identified for environmental protection. As such, we considered effects on microbes only to the extent that microbial processes affect “higher” organisms, rather than exploring potential effects on the microbes themselves. The effects assessment focused on apical endpoints that could be linked to adverse effects on populations or communities, such as survival, growth, and reproduction; biochemical and histological effects were not included. Toxicity endpoints included no-observed-effect concentrations (NOECs), lowest-observed-effect concentrations (LOECs), and x% effect concentrations (ECx values), such as EC10s, EC20s, and EC50s; ECx values for lethality are termed “LCx” values.

To focus the effects assessment on the most relevant data, criteria for inclusion or exclusion of studies considered product formulation tested, study design, data quality, and documentation of methods and results. Formulations with multiple active ingredients were excluded. Studies evaluating the efficacy of target compounds as biocides were generally excluded because, compared to more standard toxicity tests, the test durations were shorter (i.e., as brief as 15 min), doses were higher, and control exposures were not always included. Additional studies were excluded based on low control performance or inadequate documentation of methods and results. Certain studies were designated as supplemental information; these studies are summarized in Supporting Information, 4, but are not included in the quantitative risk analysis. Supporting Information studies included those with shorter than standard test durations, uncertain product formulation, test conditions that would cause bioavailability to differ greatly from field conditions (e.g., sand-only exposure media), and limited study documentation.

Toxicity data interpretation. The toxicity assessment is based on USEPA's approach to identifying “concern levels” under TSCA (Nabholz, 1991; USEPA, 1984; Zeeman & Gilford, 1993). The TSCA approach involves applying an assessment factor to the lowest toxicity test result(s). Assessment factors used to derive concern levels are selected based on the number of available species groups (algae, invertebrates, and fish) and durations (acute and chronic). To maintain transparency for risk characterization, we carry forward both components of the TSCA concern level for each target compound and exposure media, namely the toxicity value for the most sensitive species (i.e., the low-end toxicity value [LTV]) and the assessment factor, which we term the *target margin of safety*, respectively. Preserving these two components for risk calculations, rather than collapsing them into a single concern level, facilitates distinguishing issues related primarily to toxicity data gaps (i.e., high target margins of safety) from other environmental safety concerns.

As applied in the present analysis, acute LTVs are based on LC50s, and chronic LTVs are based on EC10s and NOECs. The target margin of safety for a compound in a given exposure

medium is assigned as 100 if acute or short-term chronic toxicity data are available for three trophic groups (e.g., fish, invertebrates, and algae), but chronic data are not available for the most sensitive of these groups. If chronic toxicity data, including a NOEC or EC10, are available for the most sensitive trophic group, then the target margin of safety is assigned as 10. For multiple studies with the same species, test conditions, and endpoints, we applied the geometric mean of results, consistent with USEPA's ambient water quality criteria derivation methods (Stephan et al., 1984).

For comparability with estimated freely dissolved BAC exposure concentrations, the aqueous LTV for total BAC was also converted to a freely dissolved BAC basis using NICA-Donnan modeling. Concentrations of humic matter and ionic strength were estimated for the laboratory studies underlying the LTV, for input into the model (see section *BAC effects assessment*).

Toxicity extrapolation among media. Aquatic toxicity data are available for BAC, BZT, and PCMX; but sediment and soil toxicity data are only available for BAC, and the BAC sediment toxicity data set is limited to a single study. Therefore, partitioning approaches were used to extrapolate aqueous toxicity data to sediment and/or soil. This type of extrapolation requires that the sensitivity of sediment- or soil-dwelling organisms is comparable to that of aquatic organisms, aqueous chemical concentrations in the interstitial water of sediment or soil provide a good representation of bioavailable exposures in these media, and interstitial water concentrations can be adequately estimated by assuming equilibrium partitioning between solid and aqueous phases. The first two of these premises have been extensively validated for hydrophobic organic compounds and metals, although the last tends to be a more substantial source of uncertainty because of variation in the sorptive qualities of different sediments (Di Toro et al., 1991; Kraaij et al., 2003; McDonough et al., 2010; Redman et al., 2014; USEPA, 2003b, 2005). Aquatic LTVs were extrapolated to sediment and soil using the same methods described for extrapolating surface water chemical concentrations to sediment (see section *Partitioning from surface water to sediment*), assuming an organic carbon content of 1% in sediment and 4.7% in biosolids-amended soil (median from Fuchsman et al. [2010]). We assumed the CEC in sediment and soil to be the same (20 cmol charge/kg [Bergstrom et al., 1987]).

Risk characterization

Risk characterization integrates the exposure and effects assessments to evaluate the likelihood of adverse ecological effects due to the target compounds. Margins of safety were calculated as the ratio of the LTV to the exposure point concentration. Risks are considered negligible under a given scenario if the calculated margin of safety is greater than the target margin of safety. If the calculated margin of safety is ≤ 1 , then the target compound may pose some risk, contingent on the accuracy of the exposure and effects assessments. If the calculated margin of safety is > 1 but less than the target margin of

safety, then the potential for adverse effects is uncertain, and further investigation may be warranted to fill data gaps and thereby lessen the target margin of safety. The margin of safety approach is not intended to provide a definitive conclusion regarding the extent, severity, or certainty of any predicted adverse effects. Rather, where some risk or uncertain risk is predicted, further evaluation is recommended. Further environmental monitoring is anticipated in any case to understand potential changes in environmental exposures as a result of increased antiseptic use (Hora et al., 2020). The risk characterization for the hypothetical future scenario provides a forecast of possible risks under assumed usage changes and serves as a demonstration of rigorous assessment methods, notably those applied to quantify surfactant fate and bioavailability.

RESULTS AND DISCUSSION

Commensurate with the extent and diversity of the target compounds' uses, data to support the present analysis are most extensive for BAC, followed by PCMX, and are most limited for BZT. Monitoring data are summarized in Tables 4 and 5, with complete data provided as Supporting Information, 2. Toxicity data are illustrated in Figures 3 and 4 and summarized in greater detail in Supporting Information, 4.

BAC

BAC exposure assessment. Exposure point concentrations for BAC in recent past and future scenarios are given in Table 6. Recent past exposures are characterized for surface water and sediment based on US and northern and western European data. The majority of the sediment data represent samples from either New York/New Jersey Harbor (USA)—an area notably affected by dense urbanization, industrial activity, and combined sewer overflows—or water bodies in close proximity to wastewater outfalls. One study was identified that measured BAC in biosolids-amended soils; however, only a single sample was analyzed. Therefore, biosolids data for BAC from three studies were used to estimate soil BAC concentrations (Heyde et al., 2020; Kaj et al., 2014; Östman et al., 2017; Table 5).

TABLE 4: Measured removal efficiency of benzalkonium chloride and chloroxylenol from wastewater

Treatment type	n	Removal efficiency (%) ^a		
		Minimum	Median	Maximum
BAC^b				
Standard (activated sludge)	28	86.4	99.0	99.9
Trickling filter/rotating biological contactor	2	95.9	97.4	99.0
PCMX				
Standard (activated sludge)	20	0.0	91.5	99.0
Trickling filter	1	NA	90.1	NA

^aData sources are given in Supporting Information, 2.

^bCalculated using average BAC-C12 and BAC-C14 removal efficiencies by sample.

n = sample count; BAC = benzalkonium chloride; PCMX = chloroxylenol; NA = not applicable.

TABLE 5: Summary of environmental monitoring data for benzalkonium chloride, benzethonium chloride, and chloroxylenol^a

Matrix	Units	Basis	Frequency of detection	Median ^b	95th percentile ^b	Maximum ^b
BAC						
Surface water	µg/L	T	31/40	0.088	2.2	2.6
Effluent	µg/L	T	43/47	0.15	2.4	6.4
Influent	µg/L	T	25/25	17	105	250
Biosolids	mg/kg	Dry wt	25/25	46	118	130
Sediment	mg/kg	Dry wt	92/94	0.62	8.1	27
Biosolids-amended soil	mg/kg	Dry wt	1/1	0.016	NA	NA
BZT						
Surface water	µg/L	T	0/1	<30	NA	NA
Effluent	µg/L	T	1/24	0.01	0.01	0.07
Influent	µg/L	T	0/12	<0.005	NA	NA
Biosolids	mg/kg	Dry wt	6/11	0.034	0.079	0.1
Sediment	mg/kg	Dry wt	3/9	0.006	0.23	0.36
PCMX						
Surface water	µg/L	T	31/132	0.040	0.070	0.320
Effluent	µg/L	T & D	14/14	0.20	0.77	1.1
Influent	µg/L	T	1/1	0.35	NA	NA

^aData include samples collected in the United States for all target compounds, as well as European data for BAC and BZT. Data include a combination of means and individual sample results, as reported by various data sources; details are given in Supporting Information, 2. These values were treated as equivalent for calculation of summary statistics.

^bCalculated using one-half the detection limit for nondetect results. Media with all nondetect results presented as less than the detection limit. BAC = benzalkonium chloride; T = total; NA = not applicable; BZT = benzethonium chloride; PCMX = chloroxylenol; D = dissolved.

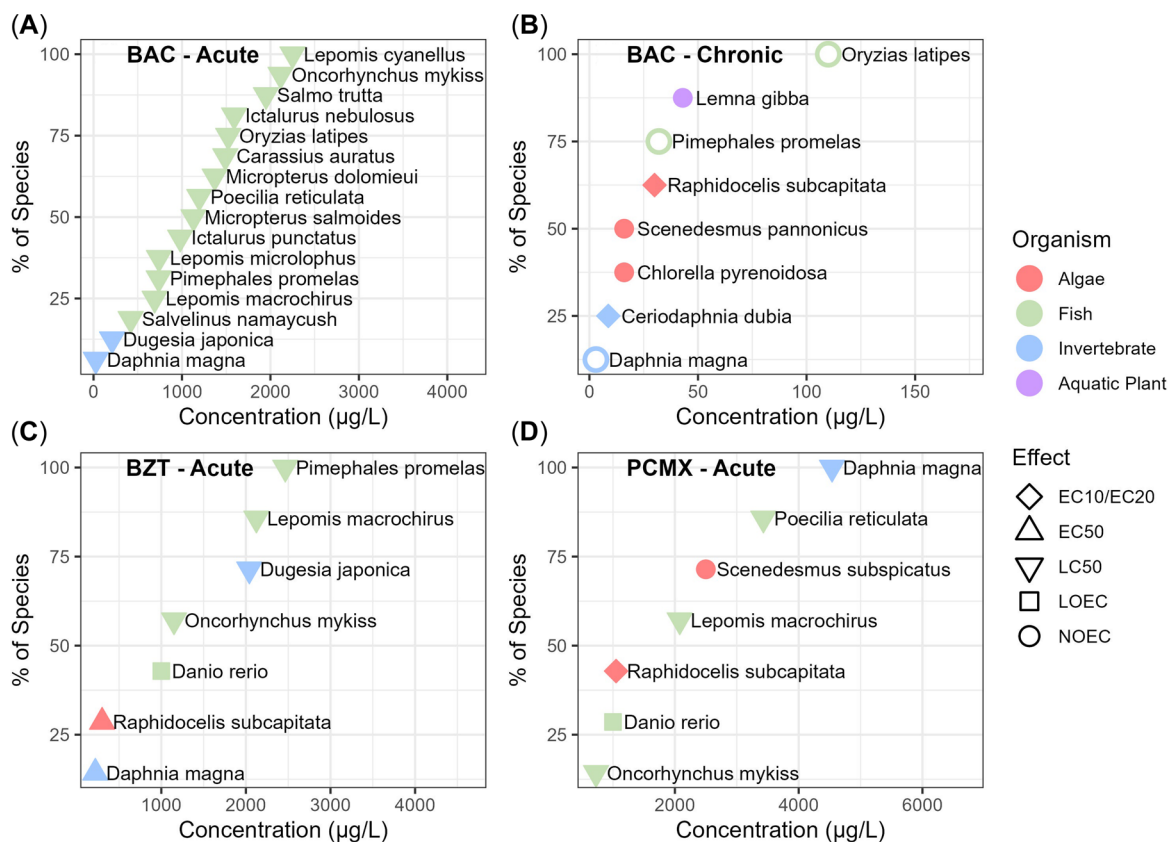


FIGURE 3: Sensitivity distributions for freshwater aquatic species exposed to (A,B) benzalkonium chloride (BAC), (C) benzethonium chloride (BZT), and (D) chloroxylenol (PCMX). Values represent 96-h mortality for median lethal concentrations (except 48-h mortality for *Daphnia magna*), 72–96-h short-term chronic growth for algae, 7–21-day reproduction for BAC chronic invertebrate tests, 34–38-day early-life stage survival and growth for BAC chronic fish tests, 7-day growth for *Lemna gibba* BAC chronic aquatic plant tests, 48-h immobilization for *Daphnia magna* exposed to BZT, and 67–91-h hatchability for *Danio rerio* BZT and PCMX tests. Open symbols indicate unbounded values (i.e., no effect at highest test concentration) or, in the case of *Daphnia magna* (BAC chronic), a geometric mean of bounded and unbounded values. EC10/20/50 = 10%, 20%, and 50% effect concentrations, respectively; LC50 = median lethal concentration; LOEC = lowest-observed-effect concentration; NOEC = no-observed-effect concentration.

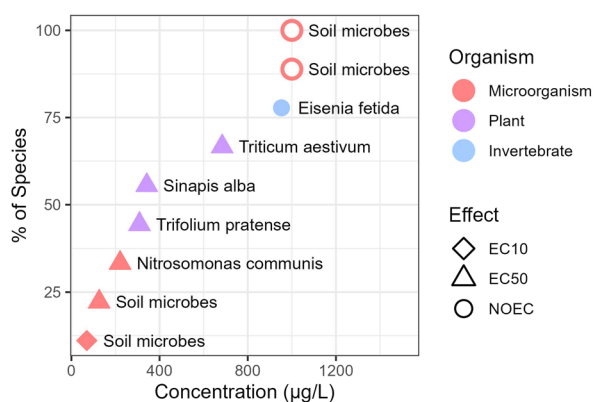


FIGURE 4: Sensitivity distribution for terrestrial species exposed to benzalkonium chloride (BAC). Studies include 16-day plant growth tests, 2–28-day microorganism nitrogen utilization tests, and 14-day invertebrate growth tests. Soil microbe results represent distinct microbial communities in various natural soils. Open symbols indicate unbounded values (i.e., no effect at highest test concentration). EC10/20/50 = 10%, 20%, and 50% effect concentrations, respectively; NOEC = no-observed-effect concentration.

Even though the future scenario assumes an increase in BAC use, the low-flow distributions of projected future BAC concentrations in surface water and sediment are similar to the distributions of monitoring data compiled for the recent past scenario (Figure 5). Two factors may contribute to the observed similarity between past and projected future distributions. First,

although the projected increase in BAC loading (based on triclosan replacement) represents approximately a 50% increase compared to median BAC loadings (based on WWTP influent data), it represents a <10% increase compared to the 95th percentile of recent past BAC loadings. Further, monitoring studies of contaminants associated with WWTPs tend to focus sampling efforts in areas likely to be affected by WWTP effluent, and monitoring results thus tend to be relatively high compared to the entirety of surface waters in the United States (see Lyndall et al., 2010).

Sorption to dissolved and particulate organic matter limits the aqueous bioavailability and toxicity of quaternary ammonium compounds such as BAC in water (Chen et al., 2014; Van Wijk et al., 2009; Versteeg & Shorter, 1992). Chen et al. (2014) found that the addition of 7 and 20 mg/L humic acids (i.e., DOC) to acute *Daphnia magna* exposure vessels increased EC50s for total BAC-C12 from 3- to 7-fold, respectively, whereas EC50s based on freely dissolved concentrations remained constant. Most laboratory exposures use aquatic media with low DOC, whereas waters in the natural environment contain appreciable levels of organic carbon and inorganic solids. Therefore, the bioavailable concentrations in laboratory exposures can be much higher than those observed in the field for the same total concentrations (DeLeo et al., 2020; Nabholz et al., 1993; NICNAS, 2016).

Freely dissolved BAC concentrations in surface water are a very small proportion of total BAC (Supporting Information,

TABLE 6: Exposure point concentrations, toxicity reference values, and risk estimates for benzalkonium chloride, benzethonium chloride, and chloroxylenol^a

Compound	Scenario	Media	Exposure point concentration		Low-end toxicity value	Target margin of safety	Margin of safety ^c	
			Median	High end ^b			Median	High end
BAC	Recent past	Surface water (total)	0.088	2.2	7.7	10	88	3
		Surface water (freely dissolved) ^d	0.0017	0.098	2.9	10	1710	30
		Sediment	0.62	8.1	430	10	699	53
	Projected future	Soil	0.29	0.74	70	10	241	95
		Surface water (total)	0.021	2.4	7.7	10	374	3
		Surface water (freely dissolved)	0.00028	0.11	2.9	10	10,400	26
	Sediment	1.2	130	430	10	358	3	
	Soil	0.72	3.2	70	10	97	22	
	Soil	0.067	NA	2800	100	41 700	NA	
BZT	Recent past	Surface water ^e	<<0.01	<<0.07	220	100	>>22 000	>>3140
		Sediment	0.006	0.23	8400	100	1 400 000	36 500
		Soil	0.00021	0.00049	2800	100	13 100 000	5 660 000
	Projected future	Surface water	0.0031	0.34	220	100	71 400	654
		Sediment	0.12	13	8400	100	71 800	657
		Soil	0.067	NA	2800	100	41 700	NA
PCMX	Recent past	Surface water	0.040	0.070	726	100	18 200	10 400
		Sediment	0.00032	0.00056	5.81	100	18 100	10 400
		Soil	0.00025	0.00095	27.3	100	111 000	28 800
	Projected future	Surface water	0.17	4.6	726	100	4180	159
		Sediment	0.0014	0.037	5.81	100	4180	159
		Soil	0.016	NA	27.3	100	1680	NA

^aUnits are micrograms per liter for surface water and milligrams per kilogram for sediment and soil. Margins of safety are unitless.

^bHigh-end represents 95th percentile of measured or modeled concentration distributions unless otherwise noted.

^cBold indicates that margin of safety is below the target but >1.

^dFreely dissolved concentrations based on median environmental dissolved organic carbon concentration (3.42 mg/L).

^eRecent past surface water BZT concentrations are conservatively represented by effluent concentrations. High end represents maximum (only) detection. BAC = benzalkonium chloride; BZT = benzethonium chloride; NA = not applicable; PCMX = chloroxylenol.

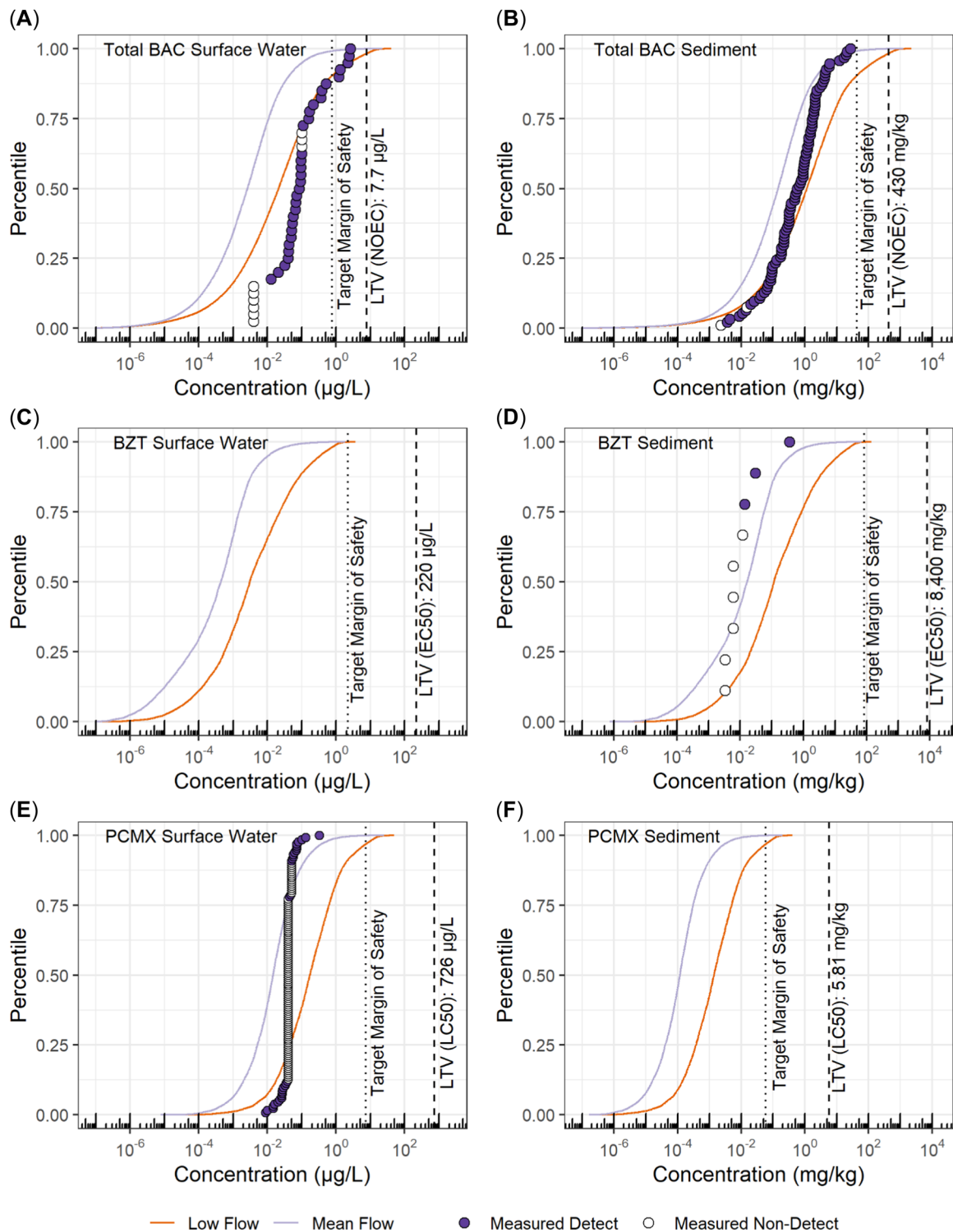


FIGURE 5: Comparison of measured (circles) and modeled (lines) exposure data distributions and toxicity reference values for total benzalkonium chloride, benzethonium chloride, and chloroxylenol in surface water (A,C,E) and sediment (B,D,F). Nondetected concentrations are represented as one-half the detection limit. BAC = benzalkonium chloride; LTV = low-end toxicity value; NOEC = no-observed-effect concentration; BZT = benzethonium chloride; EC₅₀ = 50% effect concentration; PCMX = chloroxylenol; LC₅₀ = 50% lethal concentration.

Tables S3–S5). Assuming median ionic strength and median to high-end (90th percentile) DOC, the freely dissolved fraction of BAC in surface water across recent past and future scenarios ranges from 0.3% to 4.6%. Corresponding freely dissolved exposure point concentrations range from 0.000066 to 0.11 $\mu\text{g/L}$

(Supporting Information, Tables S3–S5). The present analysis uses median to high-end DOC estimates because WWTP effluent and receiving waters are expected to be enriched in DOC. As a further sensitivity analysis, varying ionic strength from the 20th to 80th percentile of the source data extended

the freely dissolved fraction range to 0.2%–6.3% (Supporting Information, Tables S3–S5). Considering their importance to bioavailability and potential toxicity, DOC and conductivity should be analyzed in conjunction with future BAC monitoring.

BAC effects assessment. The aquatic toxicity of BAC has been extensively studied, with acute and chronic data available for a variety of freshwater and saltwater organisms (Supporting Information, 4). DeLeo et al. (2020) also compiled ecotoxicity data for BAC, but that review combined data for BAC, BZT, and related compounds; the present review is specific to BAC as defined in the *Introduction*. Figure 3 summarizes freshwater species' acute and chronic sensitivities; short-term algal studies (72–96 h) are presented as chronic because they span multiple generations for these rapidly reproducing organisms. Invertebrates are more sensitive to BAC than are fish or algae/plants, and the most sensitive species is the water flea, *D. magna*. Saltwater species' data are more limited and are included in Supporting Information, 4. Based on the available data, the sensitivity to BAC of marine fish and algae is similar to that of their freshwater counterparts, whereas marine invertebrates are less sensitive to BAC than freshwater invertebrates. The present risk analysis focuses on freshwater species because most receiving waters for WWTPs are fresh water bodies, but the results are also protective of marine species.

Most available toxicity studies evaluated BAC formulations with varying proportions of BAC-C12, -C14, and -C16. The composition of BAC mixtures could potentially affect their toxicity, but data to understand such effects are limited. Zhu et al. (2010) found that, for the green algae *Chlorella vulgaris* separately exposed to BAC-C12, -C14, and -C16, EC50s decreased (i.e., toxicity increased) with increasing alkyl chain length, although the difference was not great (20% difference between BAC-C12 and -C16). Ndabambi and Kwon (2019) reported EC50s for the green algae *Raphidocelis subcapitata* separately exposed to BAC-C8 through -C18. The authors found that EC50s of BAC-C14, -C16, and -C18 were nearly identical (6.8–7.0 µg/L) but that EC50s for BAC-C8, -C10, and -C12 were approximately 190-fold, 28-fold, and 8-fold greater (i.e., less toxic), respectively. García et al. (2001) reported 24-h EC50s for *D. magna* indicating that BAC-C14 was 40% more toxic than BAC-C16. Although BAC mixture composition might affect toxicity, the available data are too inconsistent to confidently predict compound-specific differences in toxicity.

An LTV for BAC in surface water of 7.7 µg/L is derived as the geometric mean of four chronic NOECs for effects on *D. magna* reproduction. The target margin of safety is 10 because chronic values are available for the most sensitive type of species. The underlying *D. magna* toxicity values range from a NOEC of 2.0 µg/L to an unbounded NOEC of 40 µg/L (Castro et al., 2018; Kim et al., 2020; McIntyre & Pate, 1992; National Institute of Technology and Evaluation, 2001). Lavorgna et al. (2016) presented an additional study of chronic BAC effects on *D. magna* reproduction, with an EC10 of 0.06 µg/L and a corresponding NOEC of 0.07 µg/L. There are no clear differences in test conditions between the study of Lavorgna et al. (2016) and the other four that help explain the markedly lower effect

concentration. Therefore, this result was treated as an outlier and excluded from the LTV calculation. Uncertainty associated with this exclusion is further discussed in the BAC risk characterization.

The tendency of surfactants to sorb to surfaces and dissolved organic matter can affect the reproducibility of surfactant toxicity studies. For example, subtle interlaboratory differences in feeding or test vessel dimensions can affect surfactant bioavailability, and undissolved test substance can cause surface entrapment of small organisms. Similar to the present evaluation, Rhodes et al. (1995) reviewed the chronic toxicity of phthalate surfactants to *D. magna* and identified a low outlier among multiple results for the same compound, which they recommended excluding for risk-assessment purposes.

The aqueous LTV for total BAC was converted to a freely dissolved BAC basis, for comparability with estimated freely dissolved BAC exposure concentrations, using NICA-Donnan modeling (see section *Aqueous bioavailability modeling*, and Supporting Information, 3). The concentration of humic substances in laboratory water was estimated from a DOC concentration reported for fed *D. magna* studies (1.65 mg/L [Allen et al., 2010]). In toxicity studies, *D. magna* are fed fresh organic material such as algae (see Allen et al., 2010; Castro et al., 2018; Kim et al., 2020; McIntyre & Pate, 1992), which has less potential than humic material to bind cations (Reuter & Perdue, 1977). Nevertheless, the presence of fresh organic matter has been shown to reduce toxicity in some assays (Koukal et al., 2007; McIntyre & Guéguen, 2012). The proportion of humic material-like organic carbon in the toxicity assays was thus approximated as 50% of the DOC concentration. The ionic strength of the *D. magna* test media was determined based on the reported media for each study and corresponding major ion measurements for standard test media (Loureiro et al., 2011). More cations than anions were measured, causing charge imbalance; the remaining negative charge was assigned to chloride ions. In the four toxicity studies underlying the LTV, BAC was estimated to be 30%–50% freely dissolved, resulting in a geometric mean freely dissolved LTV of 2.9 µg/L. As such, the mitigating effect of humic binding in these laboratory studies was approximately 10–100-fold less than in natural surface waters.

The assessment of BAC toxicity in sediment is informed by two lines of evidence. A single spiked sediment toxicity study provides a NOEC of 260 mg/kg and a LOEC of 520 mg/kg for 28-day growth effects in the midge *Chironomus dilutus* (England & Leak, 1995). Mortality, emergence, and development rate were also evaluated and were less sensitive than growth in the present study. In addition, the LTV identified above for BAC in surface water (based on *D. magna* chronic NOECs) can be extrapolated to sediment using the K_d identified for BAC partitioning from surface water to sediment, resulting in a sediment LTV of 430 mg/kg. This LTV is consistent with the sediment toxicity study because it lies between the observed sediment NOEC and LOEC, and it represents a much larger body of toxicity data compared to the single available sediment toxicity study. Thus, risk estimates are calculated

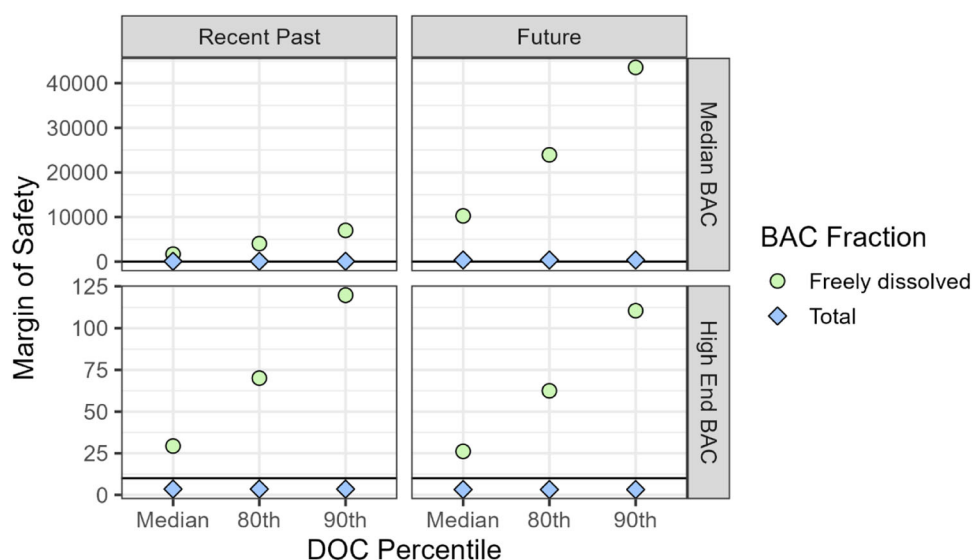


FIGURE 6: Margins of safety calculated for benzalkonium chloride (BAC) based on total and freely dissolved exposure point concentrations and low-end toxicity values. Horizontal line represents the target margin of safety (10). The median, 80th, and 90th percentile dissolved organic carbon (DOC) concentrations are 3.42, 6.98, and 10.8 mg/L, respectively. Note difference in scale between median and high-end margins of safety. Recent past median exposures, based on monitoring, are higher (lower margins of safety) than modeled future median exposures, likely because monitoring studies have focused on areas with potential BAC sources.

using the LTV of 430 mg/kg and the associated target margin of safety of 10.

Sublethal toxicity data for BAC in soil are summarized for plants, invertebrates, and microbial community function in Figure 4 (details in Supporting Information, 4). The lowest identified terrestrial EC10 is 70 mg/kg, based on reductions in nitrification by soil microorganisms (ECHA, 2013). Another study reported in ECHA (2013) found higher NOECs (>1000 mg/kg) using the same test methods and similar soil types, which indicates high variability in this endpoint. Because these studies evaluated potentially different microbial consortia, the results are not combined to calculate a geometric mean. Therefore, the soil LTV for BAC is 70 mg/kg. Based on the availability of sublethal toxicity data for plants, invertebrates, and microbial community function, the target margin of safety is 10.

BAC risk characterization. Environmental risk estimates for BAC are presented in Table 6, and distributions of surface water and sediment exposure concentrations are compared to toxicity reference values in Figure 5. On the basis of total BAC concentrations, all recent past and future BAC exposure estimates for surface water, sediment, and soil are less than the applicable LTVs; but the margins of safety are less than the target margins of safety for both high-end surface water scenarios and the projected future high-end sediment scenario. The estimated margins of safety for BAC in biosolids-amended soil are all greater than the target margin of safety.

As discussed above, the bioavailability of BAC in water can vary substantially depending on the concentrations of dissolved organic matter and other sorbents (Chen et al., 2014). Although the margin of safety for high-end concentrations of total BAC is less than the target, the margin of safety based on

the freely dissolved concentrations is well above 10 at median environmental DOC concentrations (Table 6 and Figure 6). If the surface water LTV were to be calculated using all five chronic *D. magna* studies (i.e., including the low outlier), then the high-end margins of safety for freely dissolved BAC would be approximately equal to 10. Considering the difference in safety margins estimated for total and freely dissolved BAC, future BAC monitoring efforts would benefit from evaluation of local DOC and major ion concentrations and/or passive sampler measurements of freely dissolved BAC concentrations (Chen et al., 2012; Timmer et al., 2012).

For the future scenario, the margins of safety estimated for BAC in sediment are the same as those estimated for total BAC in surface water because the same K_d value is used to extrapolate exposure and effect concentrations from surface water to sediment. The NICA-Donnan model should be applicable to interpreting BAC concentrations in sediment interstitial water, and we infer from the surface water evaluation that freely dissolved BAC concentrations in interstitial water are likely to present low risk even under the high-end future scenario. Indeed, DOC concentrations in interstitial water are likely higher than in surface water, which would further decrease BAC bioavailability. Future work could test these inferences with approaches ranging from sediment toxicity testing to passive sampler measurements of freely dissolved BAC concentrations in interstitial water.

BZT

BZT exposure assessment. We identified three studies measuring BZT in relevant environmental media (Östman et al., 2017; Pati & Arnold, 2020; Paun et al., 2018), representing data from Europe and the United States. Although BZT

was not detected in surface water or WWTP influent, some WWTP effluent, biosolids, and sediment samples contained detectable BZT concentrations (Table 5). Because of limited data, a semiquantitative recent past scenario was assessed for BZT using the available monitoring data. Recent past surface water exposures were characterized using available WWTP effluent data, recognizing that this represents a worst-case scenario because it does not account for dilution on discharge to receiving waters. Biosolids data for BZT are available from one Swedish study (Östman et al., 2017; Table 5), and those data were used to estimate soil BZT concentrations.

The future scenario assumes that much of the past use of triclosan is replaced by BZT, although to date BZT is a relatively minor component of antimicrobial usage. Because of its limited use, data to estimate BZT concentrations in consumer products relative to past triclosan concentrations are not readily available; however, anecdotal information supports a replacement ratio of 1, as assumed for this assessment. Consistent with its branched alkane structure, BZT is not readily biodegradable (no CO₂ evolution following 28 days of incubation [ECHA, 2017]), so the biodegradation rate constant was accordingly set to 0. The inherent biodegradability of BZT has not been tested, however, so this determination is conservative (e.g., see section *PCMX exposure assessment*). Based on a low critical micelle concentration, BZT is predicted to be highly sorptive (Table 2). Thus, predicted removal efficiencies are high because of transfer from wastewater to primary and secondary sludge.

BZT effects assessment. Aquatic toxicity data for BZT are limited to short-term tests, including short-term chronic data for algae and acute toxicity data for invertebrates and fish (Figure 3; details in Supporting Information, 4). No marine, sediment, or terrestrial toxicity studies were identified for BZT. Like BAC, BZT was most toxic to *D. magna* (ECHA, 2017). The corresponding aquatic LTV, representing an acute EC50 for *D. magna* immobilization, is 220 µg/L. Because no chronic toxicity data are available for invertebrates, the target margin of safety for BZT is 100.

Sediment and soil toxicity values for BZT were derived from the surface water LTV using K_d values determined from the Droge and Goss (2013a, 2013b, 2013c) cation exchange model (see section *Partitioning from surface water to sediment*). Based on the different organic carbon contents assumed for sediment and soil, the LTVs for these media are estimated to be 8400 mg/kg and 2800 mg/kg, respectively. Because of the data limitations in the underlying aquatic toxicity data set, the target margin of safety is 100.

BZT risk characterization. Table 6 presents risk estimates for BZT in a future scenario, assuming this target compound replaces a substantial portion of the past down-the-drain uses of triclosan. In all cases, the calculated margins of safety are several orders of magnitude greater than the target margin of safety. Thus, potential future risks due to BZT in these media are acceptable, given the mass loading assumed in the present analysis. Uncertainties in the present analysis include the lack of chronic toxicity data, limited environmental monitoring to date,

and limited information on environmental persistence of BZT. Further environmental monitoring could reduce uncertainty associated with aspects of the BZT exposure assessment that relied on modeling and would address pandemic-related usage increases that may differ from the triclosan replacement scenario modeled in the present study.

PCMX

PCMX exposure assessment. Extensive monitoring data are available for PCMX in surface water, largely because of the compound's inclusion in a multiyear monitoring program in the US Great Lakes region (Lee et al., 2012; US Geological Survey, 2016). Thus, recent past exposures are characterized for surface water based exclusively on US monitoring data (Tables 5 and 6). No applicable studies were identified that measured PCMX in sediments or biosolid-amended soils, and given its moderate hydrophobicity, PCMX concentrations and persistence in sediments and biosolids are expected to be limited. Nevertheless, PCMX concentrations in these media were modeled to ensure completeness of the analysis (Tables 3 and 6).

For modeling purposes, PCMX loadings to WWTPs could not be directly estimated from concentrations in influent because of limited data availability (Table 5). Loadings were therefore calculated using WWTP effluent data and removal efficiency (Table 3). The PCMX removal efficiency for the most common WWTP type (standard activated sludge) was applied.

With respect to biodegradation, multiple tests have shown that PCMX is biodegradable following microbial acclimation. Initial tests showed that PCMX was not readily biodegradable after 28 days, so follow-up testing was conducted using less conservative and more realistic test conditions according to modified Organisation for Economic Co-operation and Development (1981) 302A methods, using a semicontinuous activated sludge reactor. This test showed near complete removal or degradation of the parent compound (>98%) after acclimation of the microbial community. These results supported classification of PCMX as “inherently,” but not “readily,” biodegradable (ECHA, 2018). In addition, an extended-duration ready biodegradability study (ECHA, 2018) demonstrated a lag phase of 11–32 days while the microbial community acclimated, followed by rapid degradation of PCMX, achieving 63%–73% mineralization (ECHA, 2018). These results support classification of PCMX as “readily biodegradable (failing 10-day window),” which translates to a higher biodegradation rate constant than “inherently biodegradable” (European Commission, 2003). For the purposes of the present analysis, the more conservative option (“inherently biodegradable”) was selected to model PCMX concentrations in biosolids (Table 3). To model future PCMX concentrations in surface water and sediment, measured WWTP removal data were applied directly rather than by modeling biodegradation. Consistent with laboratory findings, PCMX removal efficiency is generally high (Table 4) but varies directly with solids retention time during treatment (Oppenheimer et al., 2007).

Recent past and projected future exposure point concentrations for PCMX are shown in Table 6. If PCMX were to fully replace past triclosan usage as assumed for the future scenario (a conservative assumption, given the use of different disinfectant compounds across products), then PCMX concentrations in environmental media would increase by one to two orders of magnitude.

PCMX effects assessment. Toxicity data for PCMX are limited to aquatic toxicity studies; no terrestrial or sediment toxicity studies were identified. The aquatic toxicity data include short-term chronic algal tests and acute fish and invertebrate toxicity studies (Supporting Information, 4). Figure 3 summarizes relative sensitivities of the species studied. In general, fish are more sensitive to PCMX than are algae and invertebrates. The LTV of 726 $\mu\text{g/L}$ represents the geometric mean of three 96-h LC50 values for rainbow trout (*Oncorhynchus mykiss*; Bionomics, 1980, 1984; Clitherow, 1991). Because only acute data are available for the most sensitive trophic group, the target margin of safety is 100.

No studies of PCMX toxicity in sediment or soil were available. Therefore, sediment and soil toxicity values were derived by estimating the solid-phase concentration of PCMX that would partition to interstitial water at a concentration equal to the aquatic LTV (i.e., equilibrium partitioning approach; see section *Toxicity extrapolation among media*). The resulting sediment LTV is 5.81 mg/kg, and the soil LTV is 27.3 mg/kg. Consistent with the target margin of safety for the surface water LTV, the target margin of safety for the sediment and soil LTVs is 100.

PCMX risk characterization. Comparing the PCMX exposure point concentrations to the applicable LTVs, all calculated margins of safety are greater than the target margin of safety of 100. A notable uncertainty in the risk characterization for PCMX is the lack of chronic toxicity data for fish. Although acute-to-chronic ratios for aquatic organisms are generally <100 for most chemicals, there are exceptions (e.g., compounds that exert toxicity through endocrine activity [Matthiessen & Johnson, 2007]). As reviewed by Exponent (2014), *in vitro* studies with PCMX indicate weak endocrine activity (see Houtman et al., 2004; Nakama et al., 2007; Nishihara et al., 2000), but *in vivo* mammalian studies have shown no effects on hormonally sensitive endpoints in intact animals (Chesterman, Heywood, et al., 1973; Chesterman, Whitehead, & Street, 1973; Doyle & Elsea, 1965; Guess & Bruch, 1986; Hunter et al., 1973; Momma et al., 1988; Morris, 2002). Because endocrine pathways are highly conserved among vertebrate species, it is unlikely that chronic *in vivo* fish studies would demonstrate hormonally sensitive effects of PCMX, when no such effects were observed in mammals. Given the high margin of safety and availability of *in vivo* mammalian data demonstrating a lack of endocrine-related toxicity, chronic fish toxicity data for PCMX are not considered a critical data gap. Thus, adverse ecological effects attributable to PCMX are considered unlikely for both the recent past and projected future scenarios.

CONCLUSIONS

Given the withdrawal of certain formerly high-use antimicrobials in part because of environmental concerns, it is important to ask whether the compounds that replace them are environmentally safe. By compiling and evaluating the available environmental occurrence, fate, and toxicity data for BAC, BZT, and PCMX, the present risk analysis provides a framework to help prioritize and interpret future data collection to more fully address that question. For PCMX and BZT, adverse ecological effects are unlikely based on recent and projected future use, with high margins of safety in the scenarios assessed. There is some uncertainty in the identification of a target margin of safety for PCMX, based on screening-level tests for potential endocrine activity. However, no endocrine effects due to PCMX are evident in tests with live mammals, suggesting that the lack of chronic fish toxicity data is not a critical data gap.

For BAC, evaluation of potential bioavailable exposures indicates that adverse ecological effects are unlikely based on the WWTP loading estimates assessed in the present study. Given the intense need for antiseptic use during the COVID-19 pandemic, further environmental monitoring is warranted to gauge the true extent of increased environmental exposures. Such monitoring should be designed to support interpretation of BAC bioavailability, whether by directly measuring freely dissolved concentrations (i.e., through passive sampling) or by measuring parameters to support bioavailability estimation, such as DOC and TOC, CEC, and aqueous ionic strength.

Supporting Information—The Supporting Information is available on the Wiley Online Library at <https://doi.org/10.1002/etc.5484>.

Acknowledgment—The authors thank S. Giolando and S. Morrall for discussions about surfactant behavior and L. Yost and D. Turnbull for discussion of endocrine effects. S. Pati and E. Olkowska provided clarifications of their research, and J. P. Gustafsson helped troubleshoot Visual Minteq implementation. D. Ferrer implemented the iSTREEM modeling. The authors also express appreciation for ACI member company representatives who provided constructive comments on earlier drafts of this assessment. The American Cleaning Institute provided funding for the present study.

Author Contributions Statement—**Phyllis Fuchsman**: Conceptualization; Supervision; Methodology; Investigation; Writing—original draft; Writing—review & editing. **Kyle Feters**: Investigation; Formal analysis; Writing—original draft; Writing—review & editing; Visualization. **Alison O'Connor**: Investigation; Formal analysis; Writing—original draft; Writing—review & editing; Visualization. **Michael Bock**: Methodology; Formal analysis; Writing—review & editing. **Miranda Henning**: Supervision; Methodology; Writing—review & editing. **Lauren Brown**: Investigation; Data curation; Writing—review & editing. **Igor Mrdjen**: Investigation; Visualization; Writing—review & editing. **Kathleen Stanton**: Conceptualization; Funding acquisition; Project administration; Writing—review & editing.

Data Availability Statement—Data are provided in the Supporting Information files and in cited papers.

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