Environmental Science & Technology

Feature

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On the Need and Speed of Regulating Triclosan and Triclocarban in the United States

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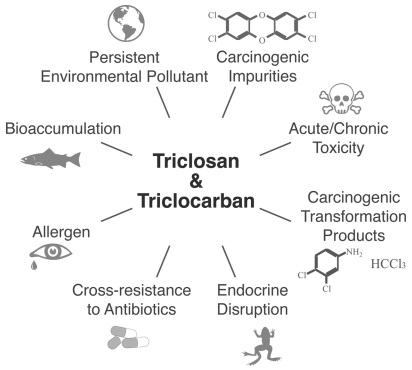

The polychlorinated aromatic antimicrobials triclosan and triclocarban are in widespread use for killing microorganisms indiscriminately, rapidly, and by nonspecific action. While their utility in healthcare settings is undisputed, benefits to users of antimicrobial personal care products are few to none. Yet, these latter, high-volume uses have caused widespread contamination of the environment, wildlife, and human populations. This feature article presents a timeline of scientific evidence and regulatory actions in the U.S. concerning persistent polychlorinated biocides, showing a potential path forward to judicious and sustainable uses of synthetic antimicrobials, including the design of greener and safer next-generation alternatives.

INTRODUCTION

Antimicrobial agents are both a boon and threat to human health, with questions about their proper design, useful application, disposal and regulatory framework looming large for scientists, the medical community, regulators and consumers of antiseptic personal care products.

In the late 1930s and early 1940s, it was discovered that the substitution on aromatic rings of hydrogen atoms with chlorine, yielded a novel chemistry of powerful biocides, including antimicrobials.[1] The resultant synthetic organohalides, which are either absent or rare in natural environments,[2,3] immediately were put to large volume, worldwide use as biocides. However, within a few years, many of these compounds and formulations showed adverse effects, including human toxicity, ecotoxicity, and unwanted environmental persistence and bioaccumulation, quickly leading to regulatory bans and phase-outs.[1,4] For example, hexachlorophene, introduced in 1948 as a binuclear aromatic organohalide carrying six chlorine substituents,[5] was banned from most uses by the 1970s.[6,7] Curiously, triclocarban (TCC) and triclosan (TCS), two persistent antimicrobials first introduced to commerce in 1957 and 1964, respectively,[8] feature a very similar chemistry (i.e., two benzene rings carrying multiple chlorines) yet continue to be produced and consumed to this day at high volume.[9,10]

Indeed, the consumption of TCS and TCC and the abundance of antimicrobial products have increased in the U.S. and abroad over the past two decades, due to relaxed regulation, aggressive and widespread advertising, and media reports driving fears of potent and sometimes lethal microbial infections acquired in everyday-life by unsuspecting victims. This multibillion dollar market has saturated supermarkets worldwide and vastly accelerated the consumption of antimicrobial products; today, TCC and more so TCS can be found in soaps, detergents, clothing, carpets, paints, plastics, toys, school supplies, and even in pacifiers, with over 2000 antimicrobial products available in 2014's $1.4 billion U.S. market alone.[9,11] Despite labeling requirements, consumer awareness of harmful active ingredients in household products remains low.[12] By contrast, TCC sees far more limited applications, mostly in bar soap formulated to concentrations of about 2% by weight, higher than the 0.1−0.5% content of TCS-enabled antimicrobial products. Consumers reaching for a random soap on U.S. supermarket shelves, likely bring home a product containing either TCS or TCC. In 1999/2000, TCS or TCC were present in 75% of liquid soaps and 29% of bar soaps in the U.S. market.[13] Today, these numbers may be even higher.

More than a decade into the accelerated use of polychlorinated aromatic antimicrobials, there now are unmistakable signs of these chemicals taking a toll on the health of the environment[14,15] and possibly on susceptible human populations.[16] This situation has drawn an increased scrutiny by agencies in the U.S., Canada[17] and abroad, including the U.S. Environmental Protection Agency (EPA),[18,19] Food and Drug Administration (FDA),[20] as well as the Centers for Disease Control and Prevention,[21] and the European Union.[10] On the state-level, efforts have begun to curtail the use of antimicrobials[22] after the discovery of TCS, TCC, and their dioxin-like chemical progeny in Minnesota's treasured water resources.[23,24]

In parallel to the discovery of environmental pollution and new health risks of antimicrobials,[25,26] concerns about the emergence of microbial pathogens resistant to multiple groups of antibiotics of medical import[27] have triggered the need for reassessing the *status quo* of antimicrobial usage.[28] The present feature article takes a look at the knowledge timeline concerning TCC and TCS, starting with their mid 20th century introduction into commerce and culminating with an assessment of today's information gaps as well as a glimpse of

Published: March 3, 2014

   dx.doi.org/10.1021/es500495p | Environ. Sci. Technol. 2014, 48, 3603−3611

what the future may hold for the age-old chemical war on microbes.[29]

How Environmental Contamination with Antimicrobials Was Discovered. Enabled by advances in analytical chemistry detection methods, most notably gas and liquid chromatography/mass spectrometry (GC-MS and LC-MS, respectively), TCS and TCC emerged as important environmental pollutants in disparate times and ways.

Triclosan—a broadspectrum bacteriostat and fungicide[30]—garnered the attention of environmental chemists soon after its large volume use in the early 1970s. After its patenting in 1964 and worldwide production, TCS was detected within 14 years as an environmental contaminant, first in U.S. wastewater, river water, and sediment,[31,32] and shortly thereafter in its methylated form, methyl-TCS, in fish from Tokyo Bay.[33] These early and subsequent environmental detections of TCS were enabled by its amenability to GC-MS analysis.[33,34] Initially, these detections went without much notice. This changed in 2002, however, when the United States Geological Survey (USGS) reported TCS as one of the top 10 contaminants of American rivers in its first national reconnaissance of 95 pharmaceuticals, hormones, and organic wastewater contaminants.[35,36]

Triclocarban—a fungicide and bacteriostat with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE)[37]—emerged as a contaminant of emerging concern (CEC) much later, enabled by LC-MS rather than GC-MS detection techniques. Contrary to TCS, TCC cannot be analyzed by standard GC methods, thereby concealing for decades TCC's presence in environmental samples acquired, extracted and analyzed for the occurrence of anthropogenic pollutants. For TCC to travel through a standard GC column and be detected, its reactive groups first need to be derivatized.[38] Relief from this conundrum arrived in 2004 with a simple LC-MS technique allowing direct detection of underivatized TCC.[39] Use of this tool on samples from Baltimore, Maryland, showed the presence of TCC in every urban stream monitored.[39] When applied to the city's groundwater, drinking water, wastewater, and sewage sludge, TCC was detected in many of these matrices and consistently in samples also containing TCS.[8] Significant co-occurrence of TCC and TCS (R^2 = 0.988) can be easily understood from their similar uses, chemical structures, and down-the-drain disposal mode. Upon entering USGS national data on TCS[35] into the forecasting algorithm, TCC emerged in 2005 as a previously unrecognized CEC that had been overlooked by environmental analysts for almost half a century; it was predicted to rank in the top 10 CECs in occurrence rate and in the top 20 in maximum concentration among 96 water pollutants.[8] Follow-up research using tandem mass spectrometry (LC-MS/MS) confirmed these predictions[40] and adoption of LC-based analytical tools by laboratories around the world quickly accelerated the discovery of TCC pollution in the environment and in humans.[41−45]

Today, TCS and TCC rank in the list of top contaminants of concern worldwide.[36] For example, U.S. streams have a 60−100% likelihood of containing detectable quantities of TCS and TCC.[8,23] TCS has been detected in drinking water resources,[14,46] 75% of urine samples representative of the U.S. population,[47] 97% of representative U.S. breast milk samples,[48] and combined TCS and TCC constitute over 60% of the total mass of 96 pharmaceuticals detectable in municipal sludge using EPA Method 1694.[49−51] Indeed, the environmental ubiquity of both chemicals has escalated such that TCS, TCC or both compounds are now detectable in house dust worldwide,[52−54] in ocean water,[55] and locations as remote as the water loop of spacecraft.[56] To understand this phenomenon of ubiquitous pollution, it is important to examine their production rates, distribution mechanisms, and long-term persistence upon environmental release. This behavior may be understood best when viewed through the lens of green chemistry[57] and engineering.[58]

Are TCS and TCC Sustainable Chemicals? Sustainably produced green chemicals serve their intended purpose without creating hazardous conditions for either people or the planet during chemical production, use, and following disposal.[1,57] Of particular concern for the EPA are chemicals featuring one or multiple of the following characteristics: (i) **P**ersistence in the environment, (ii) **B**ioaccumulation in animals and humans; and (iii) **T**oxicity to humans and ecosystems.[59,60] As with other problematic chemicals,[61] early warnings existed for decades concerning PBT properties of TCS and TCC, and the unsustainability of their large-volume uses.[33,62,63]

Life Cycle of TCS and TCC. The cradle-to-grave life cycle of TCS and TCC can be characterized as an open loop that violates multiple principles of green chemistry and engineering.[1,57,58] Structurally related to highly toxic and carcinogenic dioxins, TCS had been labeled a predioxin as early as 1993 by the U.S. EPA. Technical grade TCS contains traces of the most toxic member of the dioxin family, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (17.2 − 1,712 ng/kg), and 2,3,7,8-tetrachlorodibenzofuran (0.7 − 207.3 ng/kg).[64] Concerns over dioxins in TCS have motivated U.S. producers of antimicrobial products to source TCS from tightly monitored European chemical suppliers as opposed to lower-cost competitors in the Asian markets.[65] Furthermore, mixing of TCS with chlorinated drinking water can result in the formation of carcinogenic chloroform[66] and, upon release into surface water and irradiation with sunlight, of additional toxic polychlorinated dioxins[67] and less toxic dichlorinated dioxins, for example, 2,8-dichlorodibenzo-*p*-dioxin.[67] Similarly, TCC also contains toxic, carcinogenic manufacturing byproducts, such as 4-chloroaniline and 3,4-dichloroaniline, and can release more of these carcinogens upon chemical, physical, and biological attack.[68,69]

Durations of utility, i.e., useful lifespans, of TCS and TCC in personal care products are short, on the order of seconds,[70] but their environmental after-lives are much longer, measured at time-scales of up to several decades.[71−73] Upon disposal by consumers, both compounds are washed down the drain and typically are conveyed to municipal wastewater treatment plants (WWTPs). These facilities remove both TCS and TCC from raw sewage at a high efficiency of 97−98%,[74,75] leading to low ng/L levels in effluent discharged to surface waters.[76−83] However, removal from sewage does not necessarily equal degradation. During wastewater treatment, both antimicrobials distribute themselves preferentially into carbon- and lipid-rich sewage sludge, thereby accumulating in this abundant byproduct of biological sewage treatment.[74,75] During anaerobic sludge digestion, losses can occur as a result of biodegradation of TCS and TCC but concentrations also may increase due to a reduction in volume by gasification of natural organics to methane.[76,84] Levels of TCS and TCC in digested sewage sludge as high as 133 and 441 mg/kg dry weight, respectively, have been reported by the EPA; however, mean concentrations are closer to 16 ± 65 and 39 ± 59 mg/kg dry weight (±standard deviation), respectively.[85] Antimicrobials arriving at

dx.doi.org/10.1021/es500495p | Environ. Sci. Technol. 2014, 48, 3603−3611

U.S. WWTPs in substantial quantities (227 000−454 000 kg/y for TCC and 170 000−970 000 kg/yr for TCS)[8] are known to break through WWTPs and subsequently can harm algae in surface waters at ng/L concentrations.[86] Detected concentrations have been observed to exceed an acute-based predicted no-effect concentration (PNEC) of 4.7 ng/L in the River Elbe at 75% of monitoring locations,[36] and can accumulate in sediments to mg/kg levels,[14,71,87,88] where they may persist for several decades.[71] In the U.S., sewage sludge is either incinerated (∼15% of total volume) which can release more carcinogenic dioxins from TCS,[24,89] or deposited in landfills (∼30%) and on land (∼55%), from where antimicrobials and their carcinogenic transformation products may leach into adjacent surface water to impact the composition of microbial communities.[90,91] Antimicrobials applied as sewer sludge on land constitute a pathway for transfer of these chemicals into animal feed and crops destined for human consumption.[92−94] The volume of antimicrobials reentering the environment in sewage sludge after initial successful capture from wastewater is substantial; 57 000 ± 233 000 and 140 000 ± 211 000 kg/yr of TCS and TCC, respectively, are applied on U.S. land annually; for TCC, this is equivalent to a staggering 4.8−48.2% of its total U.S. consumption volume.[95] Crops shown to take up antimicrobials from soil include barley, meadow fescue, carrots, and pinto beans.[94,96,97]

Human Exposure to TCS and TCC. Human exposure to antimicrobials occurs mostly as a result of elective topical application to the human body. Showering for 15 min with a 0.6% TCC containing antimicrobial soaps was demonstrated to lead to concentrations in the blood of volunteers sufficiently high to potentially cause local inhibition of enzyme soluble epoxide hydrolase.[42,98] Use of TCS-containing toothpaste, typically formulated to 0.3% by weight, is another important source of human exposure.[99] Other known or suspected human exposure routes of lesser importance include the inhalation of antimicrobial-laden house dust,[52−54] consumption of contaminated drinking water,[100] and ingestion of food contaminated with antimicrobials either during the growing season[93,94] or postharvesting from antimicrobial-containing packaging materials.[101,102] Unsuspected environmental exposures to TCS and TCC have attracted attention by news media and the general public but the magnitude of these exposures is easily eclipsed by elective, topical use of antimicrobial personal care products.[42,98]

Toxicity of TCS and TCC to Humans. TCS and TCC are known toxicants but there still is a paucity of data on adverse effects in humans from elective and incidental environmental exposures.[48,99,103] Isolated early reports of infant deaths in the U.S. and Europe emphasized the need for caution but remain an anomaly, caused by misuse of antimicrobials in conditions not applicable to present day uses.[104−106] Acute and chronic health effects of TCS and TCC observed in humans and animals following exposure include irritation of eyes and skin,[30,107] sensitization to aeroallergens and food,[108] immunologic reactions such as allergies,[16,108−110] developmental and reproductive toxicity,[111−113] inhibition of muscle function,[114] as well as in vivo genotoxicity.[115] While limited, the number of studies involving human subjects is increasing.[98,104−106,108−110,116]

TCS and TCC as Endocrine Disruptors. An emerging additional toxic outcome of concern is endocrine disruption,[117] meaning an interfering of TCS and TCC with essential signaling systems in animals and humans, thereby adversely affecting development, sexual maturation, metabolism, and behavior.[118,119] Endocrine disruption was observed after exposure of male rats to TCC,[120] of rats to TCS,[121−124] and of frogs to TCS.[26] Of particular human health concern are the adverse effects of TCS on thyroid homeostasis and of TCC on reproductive health.[111,121,123,125]

TCS and TCC as Protagonists of Antibiotic Drug Resistance. A long recognized potential human health threat of antimicrobials is their ability to induce cross-resistance to medically important antibiotics in human pathogens and commensal microbes, thereby turning environmental microbial communities into a reservoir of antibiotic drug resistance.[27,63,126−128] Concerns about TCS-induced cross-resistance to antibiotics used in human medicine were voiced as early as 2001[129] and have since been substantiated by scientists worldwide.[130] Whereas TCS resistance can decrease susceptibility to as many as seven antibiotics simultaneously,[131] the applicability of such data to environmental settings and the actual risk remain uncertain.[132] Available studies concentrated on household settings[133] rather than on environmental locales, where the development and proliferation of drug resistance is more likely. One such unexplored locale is sewage sludge,[28] where an abundance of pathogens, multiple antimicrobials and extended contact times creates a large and risky setting for the emergence of drug resistance.

Ecotoxicity of TCS and TCC. Ecotoxicological risks also result for other biota enduring antimicrobial contact times that are infinitely longer than the few seconds these persistent antimicrobials reside on consumers' hands during their intended use. These unwanted long-term exposures of biota to high concentrations of antimicrobials take place in environments not targeted for disinfection.[36] In the built water environment, for example, inputs and accumulation of antimicrobials in activated sludge units during wastewater treatment are of potential concern, as it may diminish treatment efficacy and microbial diversity while also potentially creating reservoirs of drug resistance.[28] Similar risks also exist in soil environments subject to the application of biocide-laden sewage sludge. Here, as mentioned earlier, the proximity of large quantities of commensal and pathogenic bacteria with extremely high levels of antimicrobials is of particular concern, as is the uptake of the compounds into higher organisms, such as plants and animals.

Natural environments also feature multiple compartments where unwanted antimicrobial residues come in immediate and long-term contact with fauna and flora.[36] Here, the native, multicellular biota are known to be orders of magnitude more susceptible to the killing power of antimicrobials than are microorganisms.[14] Contrary to the situation described for hand washing (exposure times of a few seconds), these environmental toxic exposures are not temporal, but rather extend over the entire lifespan of aquatic and terrestrial organisms and across multiple generations. TCS and TCC are 100−1000 times more effective in inhibiting and killing algae, crustaceans and fish than they are in killing microbes.[14] Shallow sediments in surface waters receiving treated wastewater inputs are known to contain high μg/kg to low mg/kg quantities of TCS and TCC, levels that make impossible the survival and activity of many different species. Sediments also represent a latent source of antimicrobials and can release the compounds back into the water column upon disturbance. Application of sewage sludge in forestry and nonagricultural settings also can lead to decade

dx.doi.org/10.1021/es500495p | Environ. Sci. Technol. 2014, 48, 3603−3611

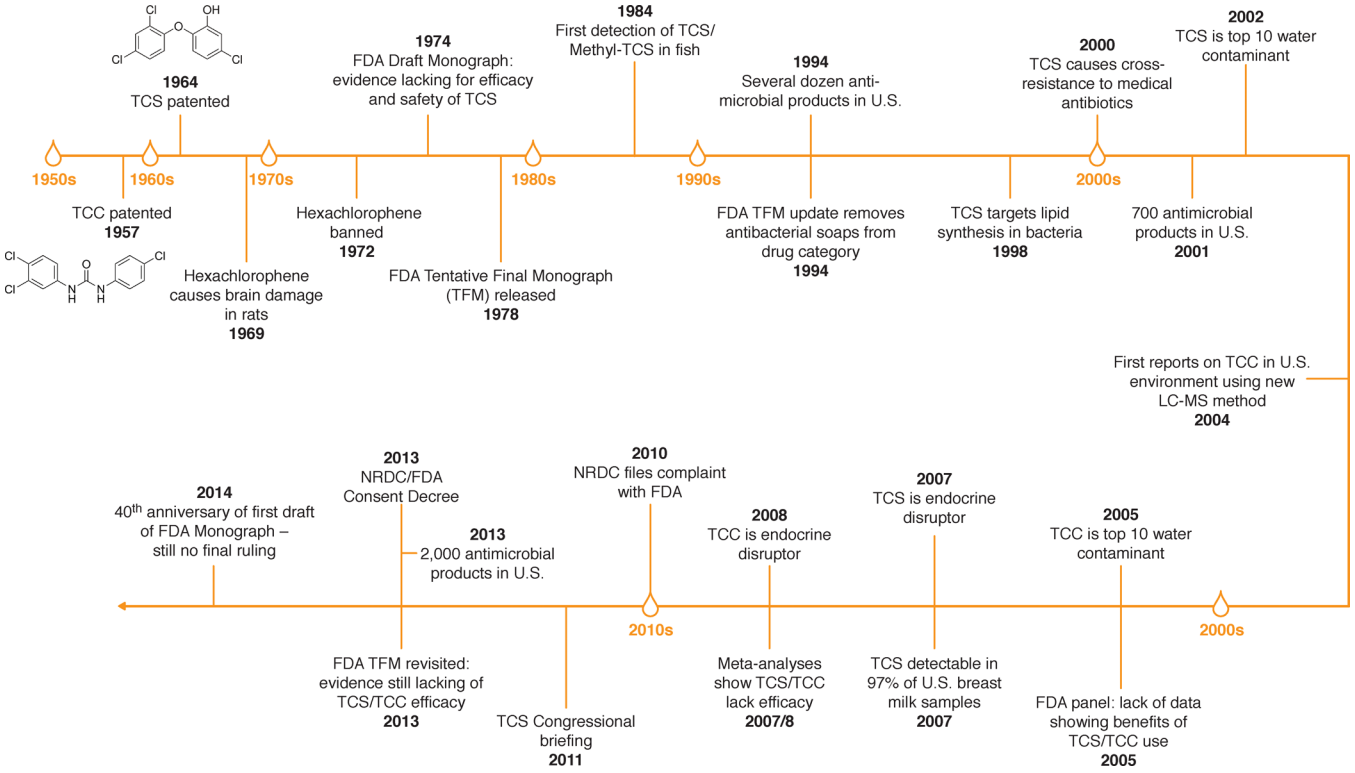

Figure 1. Timeline of scientific and regulatory events concerning the use and occurrence of triclosan (TCS) and triclocarban (TCC) in the United States, with particular emphasis on the Tentative Final Monograph (TFM) of the Food and Drug Administration (FDA).

long exposure of plants, soil-dwelling biota and their predators over multiple generations.[14,72]

Bioconcentration, bioaccumulation and biomagnification of antimicrobials have been observed in multiple organisms, including algae,[14,86] aquatic blackworms,[134] fish,[33] and even dolphins,[135] whereas affected terrestrial organisms include earth worms[72,136,137] and higher species up the food chain.[138] Documented accumulation of antimicrobials in worms and plant material and subsequent uptake by higher organisms is a known pathway for ecological risks from exposure of vertebrae, including songbirds.[15]

Bioaccumulation of antimicrobials also occurs in humans[48] but to a much lesser extent, because well-known detoxification reactions result in the rapid elimination of parental TCS and TCC.[42,98] Despite this, lipid adjusted steady-state levels of TCS in U.S. breast milk as high as 2.1 mg/kg have been reported.[48] The need for continuous elimination of antimicrobials by the human detoxification machinery has been speculated to potentially prevent expulsion of more harmful agents, such as dioxins, but scientific data are lacking.[139]

How Effective Are Antimicrobials? Although TCS and TCC are effective in killing microorganisms when applied judiciously by professionals in health care settings,[140] their proliferating use by the general population, which accounts for the vast majority of the chemicals' production volume, lacks convincing data on health benefits, according to epidemiological studies.[128,141]

These seemingly contradictory findings between antimicrobials' efficacy in clinical settings and their failure to perform in household settings can be understood easily when considering the contact time between the chemicals and their microbial targets. Thoroughly designed clinical studies reproducibly yield favorable results from hand washing times of 30 s to several minutes.[140] However, hand-washing routines of the general population differ significantly from this optimal standard. In real-world settings, the application of soaps on the hands of consumers is followed immediately by rinsing away of the active antimicrobial ingredients. Thus, for the majority of household consumers, effective contact times amount to an average of six seconds,[70] too short to provide a measurable impact on antimicrobial efficacy.

In 2005, an expert panel convened by the FDA had concluded by a vote of 11-to-1 that use of antiseptics does not provide a measurable benefit to consumers.[142] This assessment apparently has not changed in years since, as the FDA has issued in late 2013 a notice to industry of its intent to institute tighter regulations in the near future.[20]

Regulatory Framework of Antimicrobials. In the U.S., regulating TCS and TCC has been challenging over the course of the past half century, due in part to the desire to cover multiple uses and multiple compounds under a single umbrella guidance document, namely the topical antimicrobial drug products Over-the-Counter (OTC) Drug Monograph of the FDA[20,142] (Figure 1). This regulation was first drafted in 1974, tentatively finalized in 1978, and updated in 1994 but never finalized. In 2010, the Natural Resources Defense Council (NRDC) filed a complaint against the FDA in an effort to force the agency to act.[143] This legal action culminated in a consent decree, with the FDA agreeing in 2013 to finalize the monograph, at least with respect to TCS.[144] The year 2014 marks the 40th anniversary of issuance of the yet to be finalized initial draft legislation (Figure 1). In 1972, in contrast, the FDA had acted much more swiftly, by banning the antimicrobial hexachlorophene[6] over concerns of its neurotoxicity.[145] At the time, hexachlorophene-containing personal care products had multiplied in the market similar to TCS-containing formula-

dx.doi.org/10.1021/es500495p | Environ. Sci. Technol. 2014, 48, 3603−3611

tions today and adverse effects including accumulation in breast milk also had been reported for hexachlorophene.[146] Technically, the FDA could regulate TCS and TCC over environmental concerns alone but such action would be without precedence; instead, the FDA has deferred to the EPA, which regulates TCS but not TCC as registered pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[18]

Open Questions. So who should use antimicrobials? For what purpose? And what is the acceptable extent of collateral damage to ecological health and human populations? Answering these questions should best be left to public health experts, physicians, risk assessors, and sustainability scientists. Sixty years into the use of polychlorinated binuclear aromatic antimicrobials, multiple lessons can be learned from the past. Hexachlorophene was responsible for the first bloom of antimicrobial products, giving rise to over 400 hexachlorophene-containing personal care products; this episode lasted only a few years, though, before this active ingredient was banned over concerns of its neurotoxicity.[6] The second bloom in U.S. antimicrobial products from a few dozens to the current count of >2000 was triggered by the FDA's removal of antimicrobial soaps from the drug category of the Tentative Final Monograph (TFM) in 1994 (Figure 1). This history suggests that regulatory boundaries are critical in preventing imprudent uses of potentially harmful substances in personal care products.[7] Restricting nonmedical uses of TCS and TCC is an approach championed by diverse scholars and health care professionals, including the American Medical Association (AMA), the Alliance for the Prudent Use of Antibiotics (APUA), an expert group of the American Academy for Microbiology,[147] and members of the American Public Health Association (APHA).[148]

Any known and potential adverse effects of the usage of antimicrobials should be balanced with immediate and measurable benefits reaped. With respect to TCS and TCC, scientific evidence points to known benefits from their application in health care settings by health care professionals, and possibly from TCS-containing toothpaste used by individuals diagnosed with gingivitis.[149] Exclusive sale of TCS/TCC-containing soaps in pharmacies and prescription requirements for TCS in toothpaste may aid in effecting the desirable reduction in unsustainable consumption patterns and with it associated adverse effects. This tiered approach worked well for the now restricted hexachlorophene, whose allowable and prudent applications continue to this date, as a preservative at concentrations of up to 0.1% by weight. Regulations proved effective in throttling back hexachlorophene production; today, the compound is present at levels below the detection limit in U.S. wastewaters, detectable only at low concentrations (0.18–0.37 mg/kg dry weight) in raw and treated sewage sludge, where it accumulates similarly to TCS and TCC.[40]

The question of what collateral damage to people and the planet is acceptable will be informed not only by cost-benefit analyses but also by broader sustainability considerations.[1,57,58] Evidence abounds for TCS and TCC to represent nongreen chemicals whose current usage volumes are unsustainable, as indicated by large-scale pollution that needlessly places stress on the environment, animals and human populations.[36,48] These findings suggest the need for next-generation antimicrobials to overcome some of the identified shortcomings of TCS and TCC, while preserving their essential benefits.

The Future. So what will greener, more sustainable antimicrobials of the future look like? Desirable properties of next-generation antimicrobial include broad-spectrum action and high efficacy toward pathogens but low toxicity to nontarget, multicellular organisms, including aquatic and terrestrial biota and humans. Furthermore, future-use antimicrobials should have no or very low potential for fostering antimicrobial drug resistance, should undergo rapid biodegradation in conventional wastewater treatment plants, and pose no risk of bioaccumulation. Ideally, the compounds also should be sourced from renewable feedstock and lack occupational hazards during production, storage, and use. Upon disposal they should return their benign elemental building blocks to the environment, to complete a more environmentally friendly cradle-to-cradle life-cycle.[150] Studying the behavior of chemicals in WWTPs can provide helpful design clues.[95] Sustainability considerations already are informing the design of green pharmaceuticals,[151,152] and adopting this approach for antimicrobials promises to yield important benefits to people and the planet.

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Notes

The authors declare no competing financial interest.

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ACKNOWLEDGMENTS

This study was supported in part by the Johns Hopkins Center for a Livable Future and by National Institute of Environmental Health Sciences (NIEHS) awards 1R01ES015445, 1R01ES020889 and their respective supplements. The content of this work is solely the responsibility of the author and does not necessarily represent the official views of the FDA, the NIEHS, or the National Institutes of Health (NIH).

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