

Triclosen and Its Alternatives in Antibacterial Soaps

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Background: In 2017, the Food and Drug Administration banned the marketing of triclosan and triclocarban in antibacterial soaps, citing inefficacy and concerns of systemic absorption and antibacterial resistance. As a result, there is an anticipated decrease in the number of triclosan-containing products on the market with an associated increase in antibacterial alternatives (eg, benzalkonium chloride, benzethonium chloride, chloroxylenol, chlorhexidine) and cases of allergic and irritant contact dermatitis.

Objectives: The aims of the study were to determine the extent that triclosan and triclocarban are being used in the consumer and medical industries after the Food and Drug Administration marketing ban and to appraise the risk of allergic contact dermatitis to triclosan alternatives.

Methods: The National Drug Code Directory (NDCD), Google, Amazon, Target, Walgreens, Walmart, CVS, and Colorado hospitals were surveyed for antibacterial soap use. Antibiotics surveyed include triclosan, triclocarban, benzalkonium chloride, benzethonium chloride, chloroxylenol, and chlorhexidine.

Results: The most common antibiotics reported by the NDCD, consumer sites, and Colorado hospitals were benzalkonium chloride, chloroxylenol, and triclosan, respectively. Triclosan accounted for the second most prevalent antibacterial in the NDCD- and consumer site-surveyed products.

Conclusions: The triclosan marketing ban may instigate increased exposure to triclosan alternatives. The addition of antibacterial products to hand soaps does not improve soap effectiveness and may cause harm by contributing to antibiotic resistance and the development of allergic conditions. Additional studies are needed to elucidate the benefits and harms of antibacterial soaps.

Antibacterial hand soaps have a significant impact on skin health, even from an early age.¹ The hygiene hypothesis postulates that early life exposure to various pathogens and antigens may prevent a propensity of allergic inflammation. In addition, it is thought that an increase in hygiene practices may be responsible for the induction of atopic dermatitis and allergic disease. The development of atopic dermatitis and an attenuated skin barrier allows for increased penetration of sensitizing agents and increases the potential to develop allergic contact dermatitis (ACD), regardless of the antibacterial soap used.² Current literature demonstrates that there is no difference between the infection prevention provided by antibacterial soaps and plain soaps.³

In 2013, the Food and Drug Administration (FDA) asked companies that produce antibacterial soaps to prove that triclosan is

both safe and effective as an antibacterial. In 2016, after companies' inability to provide sufficient data for the safety and efficacy of triclosan, the FDA issued a statement that triclosan, as an antibacterial in soap, does not have efficacy above that of a regular hand soap. In 2017, the FDA banned the marketing of triclosan and triclocarban in antibacterial soaps, citing inefficacy of the compounds, concerns of systemic absorption, endocrine disruptions, and antibacterial resistance.⁴ A systematic review composed of 27 studies concluded that there is no additional health benefit to using triclosan-containing soaps. This review reported no reduction in infectious disease or bacterial counts among consumers using antibacterial soaps in comparison with consumers using plain soap. Furthermore, studies demonstrate that triclosan is capable of inducing cross-resistance with clinical antibiotics to at least 1 bacterial species.⁵

In light of the FDA marketing ban, there would be an anticipated decrease in the number of triclosan-containing products on the market with an associated increase in antibacterial alternatives. We aim to characterize the various antibacterial ingredients of hand soaps, appraise their safety and efficacy with respect to contact dermatitis, and note their respective properties.

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HISTORY OF ANTIBIOTICS IN SOAPS

Triclosan and triclocarban, introduced in the 1960s, were the original antibiotic ingredients included in personal care and hygiene

products. As the health impact of these substances increased, so did the search for alternative antibiotics for consumer products.⁶ Because of the FDA ruling, triclosan and triclocarban products may be phased out in favor of products such as benzalkonium chloride (BAK), benzethonium chloride (BEC), chloroxylenol, and chlorhexidine gluconate. These substitutes were postulated to be safe in their original formulations as pharmaceutical preparations and over-the-counter medicines. Although they may be replacing triclosan and triclocarban, their health impacts are poorly defined, and it is uncertain whether they are safer than the substances they are replacing. Their inclusion in personal care and hygiene products means a significantly increased frequency and magnitude of exposure in humans.

METHODS

The National Drug Code Directory

“Triclosan,” “triclocarban,” “benzalkonium chloride,” “benzethonium chloride,” “chloroxylenol,” and “chlorhexidine gluconate” were searched using the URL <https://ndclist.com/active-ingredients/>. Search results were filtered by dosage form, and the “soap,” “liquid,” “lotion,” and “solution” categories were included for the purpose of this study. Duplicate national drug codes were removed. The “aerosol,” “foam,” “cloth,” “gel,” “swab,” “ointment,” “oral,” “ophthalmic,” and “shampoo” categories that resulted from the search were excluded.

Consumer Products

For consumer items, a search query for “antibacterial soap” was performed on the following platforms: <https://www.google.com/shopping>, <https://www.amazon.com/>, <https://www.target.com/>, <https://www.walgreens.com/>, <https://www.walmart.com/>, and <https://www.cvs.com/>. The top 100 unique search results were recorded. Results were cross-referenced between 2 reviewers.

Medical Industry Products

The manufacturer and brand names of antibacterial hand soaps used in 39 hospitals within a 40-mile radius of the Greater Denver Area were obtained by contacting the supply chain management department of each hospital.

RESULTS

National Drug Code Data

Using the previous methods for the National Drug Code Directory (NDCD), there were a total of 2579 antibiotic soap products surveyed. Triclosan, triclocarban, BAK, BEC, chloroxylenol, and chlorhexidine were the antibiotics used in the available products reported by the NDCD. The most common antibacterial used was BAK (963 [37.34%]), but triclosan (945 [36.64%]) closely followed. The remainder of the data is summarized in Figure 1.

Consumer Data

In the consumer results, 110 products were surveyed using the previously mentioned search engines/retail platforms. Chloroxylenol (31) was the most common antibiotic found in the consumer search, with triclosan (27) being the second most common antibiotic found. Amazon was the only search query that resulted in products with plant-based antibacterial products. Results are summarized in Figure 1.

Medical Industry Data

Hospitals within the Greater Denver Area used a combination of triclosan and triclosan-free antibacterial hand soaps. As mentioned by supply chain management, antibacterial hand soap use is standardized throughout a given hospital system, with both inpatient and outpatient units using the same brand of antibacterial soap.

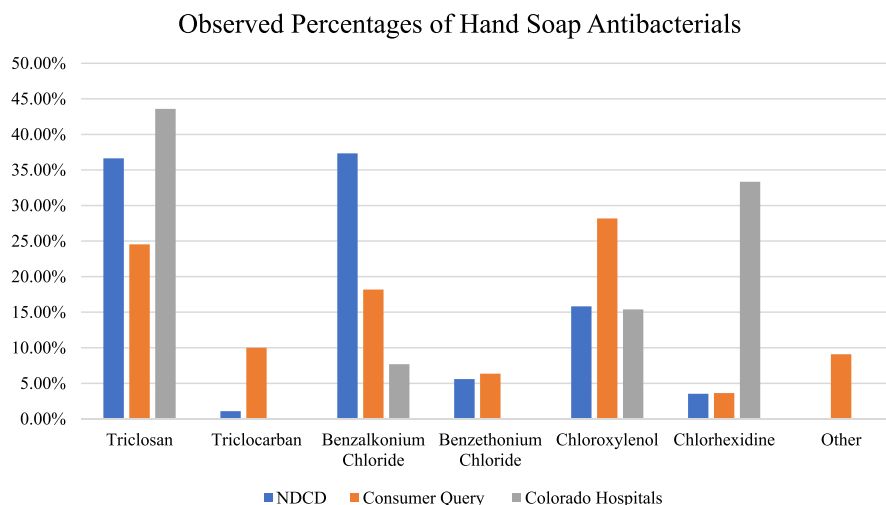


Figure 1. Results of product surveys.

Of the 39 hospitals surveyed, 17 (43.6%) used triclosan exclusively, and 22 (56.4%) used nontriclosan alternatives. Chlorhexidine (13), chloroxylenol (6), and BAK (3) were the most common triclosan-free ingredients, with chlorhexidine gluconate being the most prevalent of these triclosan-free alternatives.

DISCUSSION

The 2 major skin reactions associated with hand hygiene include irritant contact dermatitis (ICD) and ACD. The World Health Organization guidelines cite chlorhexidine, chloroxylenol, triclosan, and BAK as hand-soap antibacterial agents, which may cause ACD; however, contact allergy reactions are rare, and irritant reactions are more likely to occur.⁷ After the implementation of the 2017 FDA ban on triclosan/triclocarban marketing, there is an anticipated rise in the use of alternative antimicrobials in consumer products and an associated increase in ACD. There are relatively few studies addressing the previously mentioned antibacterials and ACD; therefore, this study looks to characterize the current state of the antibacterial market and its possible association with ICD and ACD.

The NDCD is the result of the Drug Listing Act of 1972, which requires institutions to report product ingredients to the FDA. As a result, products are provided a unique, 3-segment national drug code. This database provides a broad scope for the current status of antibiotic ingredients in soap products. Furthermore, it provides a snapshot of the transition from triclosan-/triclocarban-containing products to antibacterial substitutes. Although it is uncertain whether the number of triclosan-containing products has decreased since 2016, the ruling certainly has not eradicated triclosan use.

Many manufacturers have formulated triclosan-free antibacterial hand soaps, likely as a result of the FDA marketing ban. However,

there remain a large percentage of triclosan-containing products registered on the market, per the NDCD. Furthermore, there is concern about the safety and efficacy of the following alternative antibacterials: BAK, BEC, chloroxylenol, and chlorhexidine gluconate. Follow-up studies will be necessary to determine the long-term adverse effects of these alternative hand soaps.

With the anticipated increase in ACD to antibacterial products, it is necessary to thoroughly scan hand soap ingredients to avoid contact with confirmed allergens. However, there is a lack of transparency in disclosure of the full ingredient list found in antibacterial soaps. Although major distributors (eg, Target, Walmart, Amazon, and Walgreens) will include high-quality pictures of the ingredients list, most retailers generally do not include pictures of the ingredients or provide poor-quality images that cannot be read on a web browser. Although it is possible to find ingredient lists online or via the NDCD, these methods are not intuitive for the general public. One interesting observation that has occurred, in light of the FDA ruling, is that companies will now advertise products as “triclosan free.” Although companies are legally required to report active ingredients to the NDCD, distributors of these products are not held to the same standards of transparency and accessibility, making it difficult to identify potential irritants and allergens.

Antibiotic Considerations in Contact Dermatitis

Triclosan/Triclocarban

Since the 1960s, triclosan has been the primary antibacterial agent in both hospital and consumer hand soaps. A national survey demonstrated that triclosan and triclocarban were detected in 76% of liquid soaps and 29% of bar soaps used nearly 12 years ago.⁸ Triclosan, a diphenyl ether, and triclocarban, a derivative of triclosan (highlighted in Fig. 2), are commonly found in antibacterial hand soaps that are

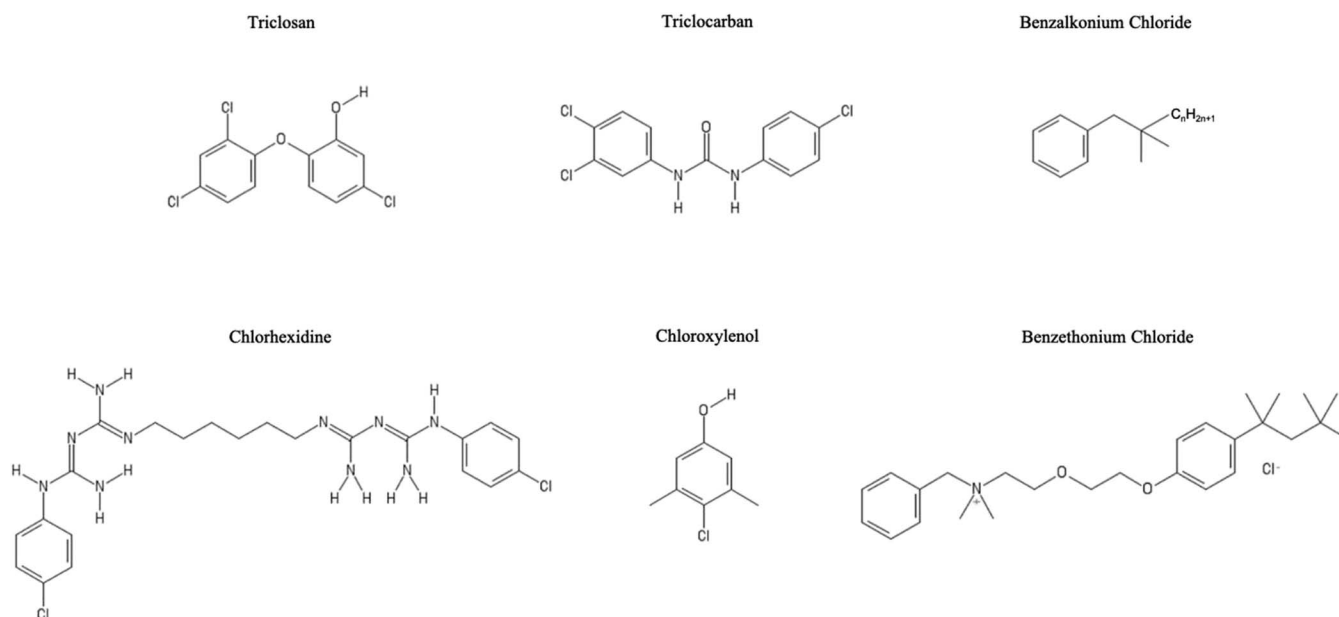


Figure 2. Chemical structures of antibacterial products.

sold for household or antiseptic use in the health care industry. Between the two, triclocarban is sparsely used, and its clinical impact is less known. Further studies are necessary to evaluate the difference in sensitization potential, allergen penetration, and irritant potential between triclosan and triclocarban. Triclosan is also found in sunscreens, dish soap, facial cleansers, toothpaste, and cosmetic products. It is a small synthetic lipophilic compound readily absorbed into the skin (Fig. 1).⁹ Triclosan eliminates gram-positive and gram-negative bacteria and is noted for its ability to target spore-forming bacteria and viruses.⁴ The FDA questions the safety of triclosan because of recent scientific research on hormone imbalances and increased bacterial resistance being associated with triclosan.¹⁰ More specifically, in vivo and in vitro studies have demonstrated that triclosan and triclocarban can interfere with thyroid hormone action, reduce levels of reproductive hormones (eg, testosterone, luteinizing hormone, follicle-stimulating hormone), cause implantation failure, and result in spontaneous abortion.¹¹ In addition, hay fever and allergies in humans have been associated with triclosan.¹

Despite triclosan's widespread appeal as an antibacterial agent, triclosan has been linked to several incidences of ACD since the 1970s. There have been reports of dermatitis exacerbated by triclosan-containing liquid soap in both consumer and medical settings, as confirmed by patch testing.¹² Although limited in occurrence, the full spectrum of triclosan-induced contact dermatitis cases is likely not fully appraised because of the lack of extensive patch testing with triclosan, particularly in health care workers.

Benzalkonium Chloride

Benzalkonium chloride is a quaternary ammonium cationic detergent that works strongly against gram-positive and gram-negative bacteria.¹³ It is commonly found in health care, personal care (eg, eyedrops), and household products. Its role in ICD is well documented^{14,15}; however, BAK's impact as an allergen is still uncertain, largely because of the number of irritant reactions read as false-positive. After 2006, the North American Contact Dermatitis Group removed BAK from their standard series because of its high rate of false-positives. However, clinical data and previous case reports lend the notion that BAK is a contact allergen, albeit rare.^{15–18} Health care workers, in particular, seem to be at an increased risk of developing BAK allergy.^{16,19,20} Furthermore, a study reports that health care workers had a 7.5% relevant reaction rate to BAK, as opposed to a relevant reaction rate of 2.3% for non-health care workers.¹⁹ Benzalkonium chloride is recognized to have significant cross-reactivity with BEC, a compound often included in female hygiene products.²¹ Other products that contain BAK include antifungals, detergents, adhesive tapes, topical creams, and ethanol.²¹

Benzethonium Chloride

Benzethonium chloride is also a quaternary ammonium compound often included as a preservative and antibiotic ingredient. As an antimicrobial, it is effective against a broad spectrum of bacteria, fungi, molds, and viruses.²² Although BAK has been available for more

than 60 years, BEC is a much newer ingredient. Benzethonium chloride is recognized to be a contact irritant, but its prevalence as an irritant is unknown.⁹ Similar to BAK, BEC is a rare sensitizer with cases of ACD to BEC-containing perfume and a BEC-containing emollient reported in the literature.²³ In a 142-patient study addressing the prevalence of BAK and BEC allergy, 1 had a definite allergic reaction and 13 had a possible allergic reaction to BAK and/or BEC.⁹ This study further concludes that if reaction to BAK is suspected, coreaction with BEC should be considered.

Chloroxylenol

Chloroxylenol, also called *p*-chloro-*m*-xylenol (PCMX), is a halogenated phenolic preservative with antibacterial activity (primarily against gram-positive bacteria).²⁴ In addition to its use in soaps, it can also be found in cosmetic products and electrocardiograph paste.¹⁰ Chloroxylenol is not a strong sensitizer, but when positive, it is usually highly relevant. In a study, the rate of positive reactions in referred patients was 0.4%.²⁵ In addition, chloroxylenol is recognized to cause ICD.⁷ In a study by Warshaw et al,²⁶ chloroxylenol was among the most prevalent contact allergens in health care workers. *p*-Chlorocresol is a related antiseptic compound, differing from PCMX in structure with an additional methyl group in the meta position. Although it is not as widely used as PCMX (only 5 products listed in the NDCD), it is recognized to have moderate allergenicity.²⁷

Chlorhexidine

Chlorhexidine is a synthetic bisbiguanide that is widely used for its low cost and high efficacy. It is most often used as an antiseptic in the medical industry preoperatively in both patients and health care providers. It has a broad antibacterial coverage, noted to be effective against gram-positive bacteria, gram-negative bacteria, and fungi. Although triclosan is noted to affect spore-forming bacteria and viruses, chlorhexidine does not.¹³

Multiple sensitivity reactions, including type I hypersensitivities, fixed drug eruptions, and photosensitivity reactions to chlorhexidine have been reported, with fewer reports of ACD.^{28–31} In a study, sensitization rates ranged from 2% to 5.4%.³² It should be noted that these patients were selected based on a pertinent history and that this percentage may not be representative of the general population.²⁸ That said, patients should be educated about chlorhexidine allergy. Other products recognized to contain chlorhexidine include corticosteroid creams and hygiene products.³¹

Plant-Based Antibacterial Products

For the last 3 decades, the use of herbal medicines and “natural” products has expanded rapidly all over the world. Although the use of plant-based products is not new to medicine, many developed countries are experiencing a surge in complementary and alternative medicines.³³ This trend has spilled over into pharmaceuticals, cosmetics, and soaps. In the search for antibiotic alternatives, specific active compounds (eg, quinones, alkaloids, essential oils, flavonoids) or secondary metabolites are starting to be used in consumer

TABLE 1. Plant-Based Products With Reported Antibacterial Activity

Plant-Based Antibiotic	Affected Organisms
<i>Aloe vera</i> ³⁵	Gram-positive and gram-negative organisms, fungi, and viruses ^{36,37}
Citricidal*	Gram-positive and gram-negative organisms ³⁸
<i>Eucalyptus</i> ³⁹	Gram-positive organisms ⁴⁰
Lemongrass ⁴¹	Gram-positive and gram-negative organisms, yeast, and fungi ⁴²
Lime ⁴³	Gram-positive and gram-negative organisms ⁴⁴
Olive ⁴⁵	Gram-positive organisms ⁴⁶
<i>Origanum vulgare</i> *	Gram-positive organisms ⁴⁷
Peppermint ^{†41}	Gram-positive and gram-negative organisms, fungi, viruses ^{48,49}
Rosemary ⁵⁰	Gram-positive and gram-negative organisms ⁵¹
Spearmint ⁵²	Gram-positive and gram-negative organisms ⁴⁹
Tea tree ⁵³	Gram-positive and gram-negative organisms, protozoa, fungi, viruses ⁵⁴
<i>Thymus vulgaris</i> ⁵⁰	Gram-positive organisms ⁵⁵

*Not associated with cases of ACD.

†Present on the ACDS Core Allergen Series.

products. In our search for antibiotic hand soaps, there were several products that contained plant-based antimicrobials (Fig. 1).³⁴ Current literature cites cases of ACD to each of the antibacterial products except citricidal and *Origanum vulgare* (Table 1). Interestingly, tea tree and peppermint oil are the only plant-based antimicrobials included in the American Contact Dermatitis Society Core Allergen Series.

Only the Amazon query, a market geared to general public, resulted in products that contained plant-based ingredients that were marketed to have antibacterial properties. This observation may be representative of the consumer shift toward “natural” products. Products will advertise that they are “triclosan-free” and will cite various plant products as their active antibacterial ingredient. Table 1 lists the plant ingredients, with reported antimicrobial activity.

LIMITATIONS

Our study was limited to the review of the active antibacterial ingredients in antibacterial hand soaps and did not include a review of other potential allergens in soaps because this has been previously reported.⁵⁶ The NDCD provides only a snapshot in the landscape of antibiotic use in soaps. This study is unable to provide a rate to which triclosan is being phased out, and further studies will be necessary to elucidate trends. Limitations of this study include the inability to confirm ingredients listed online, because they may be subject to error or reformulation without announcement. Hospital sites sampled in this study were limited to facilities located within a 40-mile radius near the Greater Denver Area. Regional differences in soap choices may not reflect nationwide trends. However, a variety of both academic and private hospital facilities were sampled,

providing insight to the diversity of hand soap use within the medical industry. Lastly, this study addressed antibacterial hand soaps but did not include other forms of hand hygiene, such as hand sanitizers. Further studies are necessary to address the impact the FDA ruling has on hand sanitizers.

CONCLUSIONS

The triclosan marketing ban, and the surge of “triclosan-free” advertisements, may instigate an increased exposure to plant-based antibacterial products and antibacterial alternatives, such as chlorhexidine, chloroxylenol, BAK, and BEC. The addition of antibacterials to hand soaps does not improve soap effectiveness and may even cause harm by contributing to antibiotic resistance and the development of allergic conditions. Furthermore, alterations in the skin microbiome may also be effected and impact skin health. Nevertheless, the continued use of antibacterial hand soaps in medical and home settings is likely. Additional studies are needed to elucidate the benefits and harms of antibacterial soaps.

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