Preserving Safety: Exploring Safer Alternatives to Phenoxyethanol In Laundry Detergents And Soaps

Greener Solutions Fall 2024

ECOS
Plant Powered Clean

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Abstract

This report presents recommendations for alternative preservatives in laundry detergent, hand soap, and dish soap. We aim to identify safer preservatives with similar or lower human and environmental health hazards than phenoxyethanol and retain or improve its efficacy. Methylisothiazolinone (MIT) is included for comparison as a commonly used preservative. In collaboration with ECOS, we established key parameters for preservative selection, including pH compatibility, maintenance of product viscosity, enzyme stability for detergent efficacy, and overall product performance (foaming, stain removal, hand feel, grease-cutting). A comparative hazard assessment was conducted using the GreenScreen for Safer Chemicals approach, identifying alternative preservatives from food preservative lists, other soap/detergent companies, the Environmental Protection Agency (EPA) Safer Chemical Ingredients List, the cosmetics/skincare industry, alternative production systems/chemical literature, and ECOS's 2015 list of potential alternatives. Our research identified seven preservative strategies: carboxylic acids, natural alternatives, peptides, hydroxamic acids, esters, polyols, and phenyl alkyl alcohols. For each strategy, we provide an inspiration, overview, technical performance, human and environmental health performance, and remaining questions. Additionally, we propose two alternative strategies: solid formulations (powder or tablet) due to the absence of water in their formulations, which therefore does not require as many preservatives as water-based products, and machine learning for discovering novel preservative-booster combinations. The report concludes by highlighting four viable options: carboxylic acids (proven, affordable, require low pH), peptides like ε-poly-L-lysine (low toxicity, but costly), esters such as sorbitan caprylate (low hazards, but low efficacy), and phenyl alkyl alcohols, particularly benzyl alcohol (effective, but higher hazards). Each option requires further exploration regarding formulation compatibility, consumer perception, and partner-specific viability.

Keywords: Preservative, Phenoxyethanol, Cleaning Products, Hazard Assessment, Environmental Health

1. Introduction

Background

Soap and Laundry Detergent Function and Usage

Laundry detergents are designed to clean fabrics and break down dirt, oils, and stains in clothing, bedding, towels, and other washable fabrics. They typically contain surfactants that lift grime away from fibers, along with enzymes to target specific stains (like protein or grease), and sometimes bleach or fabric brighteners. Soaps such as dish soap and hand soap are generally made to clean the skin or surfaces by emulsifying oils, allowing them to be rinsed away with water. Hand, body, and bar soaps for personal use focus on removing dirt and bacteria from the skin. Dish soaps are formulated for grease and food residue on dishes, and some multipurpose soaps are suitable for various surfaces around the home.

Why are preservatives needed?

Preservatives are needed in any liquid-based product to preserve the products they are added to and ensure long-term efficacy. Their main purpose is to prevent the growth of bacteria, and fungi.[1] Because the high water content of laundry detergents and soaps creates an ideal environment for the growth of microorganisms, the use of preservatives is required.[2] Without preservatives, water-based products would experience physicochemical degradation, have a short lifespan, and could become a breeding ground for bacteria that could be harmful to human health.[1,3]

The most commonly used preservatives in detergents, shampoos, conditioners, and soaps are phenoxyethanol and methylisothiazolinone (MIT). Although MIT is still commonly used as a preservative, some companies are substituting it with phenoxyethanol due to MIT's higher hazard profile.[1] Phenoxyethanol is considered safe by many authoritative bodies when used at 1%.

Current Preservatives Used

MIT (Methylisothiazolinone)

Methylisothiazolinone (MIT) is an antimicrobial agent registered by the U.S. Environmental Protection Agency (EPA) in 1977 (Figure 1.1).[4] It is used to control bacteria, fungi, and algae. It is commonly applied in household cleaning products, cosmetic beauty products, pulp/paper mills, cooling systems, adhesives, paints, and wood products to inhibit microbial growth.[4] MIT, as a preservative in cosmetics and personal care products, can be used up to 0.01% in concentration.[4]

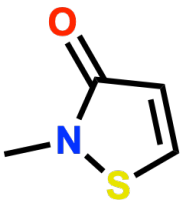

Figure 1.1. Chemical Structure of MIT

Human health impacts regarding MIT indicate moderate to high acute toxicity, particularly via inhalation and dermal exposure (Table 1.1). Chronic studies classify it as "Group D" (not classifiable as to human carcinogenicity), and risks are manageable with Personal Protective Equipment (PPE).[5] The environmental impact of MIT includes moderate toxicity to birds and very high toxicity to aquatic organisms. The occupational exposure risk to MIT can be

mitigated with proper PPE, including gloves, long sleeves, and protective eyewear for all handlers during production.

Table 1.1. Hazard table for MIT, one of the incumbent preservative chemicals.

	Human Health Group I					**Human Health Group II**									**Environmental Health**		**Environmental Fate**		**Physical Hazards**	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
MIT [6]	*L*[7]	**L**[8]	**L**	**L**[9]	DG	**vH**	M	DG	**L**	M	**H**[10]	*L*[11]	**vH**[12]	**vH**	**vH**	**vH**	*L*	vL	*L*	*L*

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Although MIT's health risks can be mitigated during manufacturing, the end-use products are in personal care and cosmetic products when end-users are dermally exposed repeatedly. The toxicity assessment for MIT is from an informal study conducted by the EPA, displaying severe eye irritation and severe skin irritation for dermal application.[4] [5] The bioaccumulation of MIT in drinking water was tested for oral ingestion at 225 ppm in drinking water for three months, which resulted in a decrease in body weight and food consumption.[4] Due to MIT's corrosive nature, it is impossible to observe that the results of mutagenicity and carcinogenicity are equivocal, hence, classified as a Group D carcinogen, as in not classifiable as to human carcinogenicity.[4]

Considering the fate of MIT in the environment and animals, the EPA has mandated strict labeling standards for products containing MIT. For example, all end-use products with MIT must have the following application restriction, "Do not apply this product in a way that will contact workers or other persons," and the following skin sensitization warning on all products, "This product may cause skin sensitization reactions in some people," to ensure consumer safety.[4]

Phenoxyethanol

Some industries are responding to the health concerns surrounding MIT by switching to phenoxyethanol as a safer alternative (Figure 1.2). Phenoxyethanol is an aromatic glycol ether naturally produced in green tea but synthesized in laboratories through the combination of ethylene oxide and a phenol.[13]

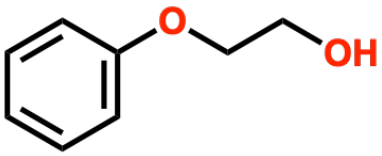

Figure 1.2. Chemical structure of phenoxyethanol

Phenoxyethanol exists among the group of phenolic compounds that have an antimicrobial effect. Phenoxyethanol serves not only as a preservative but also as a solvent for many of these products.[1] As a preservative, phenoxyethanol is effective through disrupting the cellular membrane of microorganisms, causing cell leakage and eventual cell death. Studies examining this effect have found that it permeabilizes

and solubilizes the plasma membrane in both gram-negative and gram-positive bacteria. It also has demonstrated an ability to inhibit microbial DNA and RNA synthesis.[1]

Although phenoxyethanol is considered a safer alternative, there are still some concerns regarding skin sensitization, developmental toxicity, acute toxicity, systemic toxicity, and neurotoxicity (Table 1.2). Eye irritation is the only one of these hazards of high concern. Notably, both the US Food and Drug Administration (FDA) and the European Commission's Scientific Committee on Consumer Safety (SCCS) have deemed phenoxyethanol safe for use in concentrations of up to 1%.[1]

Table 1.2. Hazard table for phenoxyethanol, one of the current chemicals used as preservatives.

	Human Health Group I					**Human Health Group II**									**Environmental Health**		**Environmental Fate**		**Physical Hazards**	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[14]	**L**	**L**	L	**M**[15]	*L*	**M**	M	**L**	**M**	*L*	**L**	*L*[16]	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	**L**

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Another hazard from phenoxyethanol occurs during its synthesis, in which phenol is ethoxylated with ethylene oxide–a known carcinogen. If ethylene oxide leaks during this process, it could cause cancer in those who are chronically exposed.[17] On April 9, 2024, EPA announced a final rule that will limit emissions of ethylene oxide from chemical plants to protect those who live near the plants.[17] Although the major concern with ethylene oxide is its use in sterilizing plants, EPA also recognizes that it is a threat to worker safety and communities surrounding the chemical manufacturing plants. In a report from 2005 by the US Occupational Safety and Health Administration (OSHA), it is estimated that there are 1100 workers producing ethylene oxide and 4000 workers who use ethylene oxide to make chemical derivatives, both of which are relevant to the life cycle of phenoxyethanol.[18]

Boosters

Laundry detergent, hand soap, and dish soap companies often incorporate boosters with preservatives to enhance the antimicrobial effectiveness of products. Also known as potentiating agents, these boosters serve various functions—a wider antimicrobial spectrum and lower concentrations. For example, while one preservative might be effective against bacteria, another might be more effective against fungi. A wider spectrum refers to the ability to effectively target a broader range of microorganisms. Combining boosters with preservatives results in a more comprehensive defense against various microbes. Reduced concentration of preservatives can potentially mitigate irritation or sensitization risks.[19] However, further research is necessary to

elucidate the specific interactions between preservative boosters and the preservatives themselves to confirm this hypothesis and optimize formulations.

ECOS uses caprylyl glycol as a booster. It is a versatile ingredient commonly employed in cosmetic and personal care formulations as a humectant, emollient, and preservative booster. Caprylyl glycol and phenoxyethanol in combination improve the overall antimicrobial effectiveness of the formulation by providing a broader spectrum of activity against various microorganisms.[20] The mechanism of action of the two preservatives together is not fully understood, and more research is needed to understand the additional benefits of this combination besides the antimicrobial efficacy.

Another booster used in ECOS's products is ethylhexylglycerin. Combining phenoxyethanol and ethylhexylglycerin demonstrates a synergistic effect in antimicrobial action. Phenoxyethanol alone acts on multiple cellular targets, inhibiting DNA and RNA biosynthesis leading to cell death at higher concentrations. When combined with ethylhexylglycerin, the antimicrobial efficacy is significantly enhanced. Initially, it was hypothesized that ethylhexylglycerin, acting as a surfactant, altered bacterial surfaces to facilitate phenoxyethanol penetration.[19] However, the exact mechanism of this synergy remains understudied. Current understanding suggests that ethylhexylglycerin weakens bacterial cell defenses, allowing phenoxyethanol to enter more easily and cause more extensive damage. This combination results in a more potent antibacterial effect than either compound used independently.[19]

ECOS uses ethylhexylglycerin with phenoxyethanol in dish and hand soaps at a concentration of 0.09% and 0.078% and caprylyl glycol with phenoxyethanol for enzyme laundry detergents at a concentration of 0.2% (Table 1.3).

Table 1.3. Table of phenoxyethanol and boosters used in ECOS products. Source: ECOS.

Booster	ECOS' Product	Preservative Concentration
Caprylyl glycol		Phenoxyethanol (1%), boosted with caprylyl glycol (0.2%)
Ethylhexylglycerin		Phenoxyethanol (0.81%), boosted with ethylhexylglycerin (0.09%)
Ethylhexylglycerin		Phenoxyethanol (0.702%), boosted with ethylhexylglycerin (0.078%)

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2. Approach

Our investigation focused on identifying alternatives for preservatives that can be used in laundry detergents, dish soaps, and hand soaps to replace phenoxyethanol, the current ECOS preservative used, and also MIT, a preservative widely used by other companies. Some parameters considered during our assessment of potential alternatives include antimicrobial properties, effective pH range, enzyme compatibility, and overall efficacy.

Antimicrobial Properties: The antimicrobial properties of a preservative are related to its ability to inhibit or prevent the growth of microorganisms such as bacteria, fungi, and mold. These preservative properties are crucial for maintaining the quality, safety, and shelf life of laundry detergents, hand soap, and dish soap.[1] One convenient measure for the antimicrobial activity of a preservative is the Minimum Inhibitory Concentration (MIC). MIC is defined as the lowest compound concentration that prevents microbial growth in vitro[2]. This is typically measured in µg/mL, which is equivalent to mg/L. The preservative of choice would ideally have low MIC values against bacteria and fungi of interest, especially *P. aeruginosa* (industrially-relevant pathogen of concern) and *Aspergillus* species (mold). A more relevant method is antimicrobial challenge testing, such as USP <51> challenge testing. This testing involves inoculating a relevant formulation with a large microbial population to mimic microbial contamination. The microbial population (in CFUs) is then counted over time, and for bacteria, the population needs to have a 2-log decrease in CFUs, while for fungi, the population should have no increase from the initial inoculated amount.[3] The species tested are *Aspergillus brasiliensis* (mold), *Candida albicans* (yeast), *Pseudomonas aeruginosa* (gram negative bacteria), *Escherichia coli* (gram negative bacteria), and *Staphylococcus aureus* (gram positive bacteria).

pH range: The acidity or alkalinity of solutions is typically measured using pH, which is a logarithmic scale that measures the concentration of protons in solution and is typically in the range of 0 to 14. A pH value below 7 indicates an acidic solution, while a value above 7 indicates a basic solution, which can also be referred to as alkaline.[4] A pH of 7 represents a neutral solution. For the products we are considering, such as detergents and soaps, the pH range is usually more alkaline,[5] but this can vary from brand to brand.

Enzyme compatibility: Certain detergent formulations contain specialized enzyme blends that break down specific types of stains and soils on fabrics. These enzymes work with other detergent components to increase cleaning efficiency, allowing effective stain removal at lower temperatures and with less mechanical agitation.[6] When considering components of a formulation that contains enzyme, care must be taken to not include chemicals that can destroy these enzymes or even chemicals that can be destroyed by these enzymes.

ECOS' requirements for alternative preservatives included:

I. Preservatives must be effective in neutral to slightly basic pH.
   A. pH Laundry Detergents: 6-8.5
   B. pH Dish Soaps: 7-9
   C. pH Hand Soaps: 6-8
II. Maintain product viscosity (typically 500-1400 cp using a Brookfield viscometer, 50rpm).
III. Ensure enzyme stability for detergent efficacy.
IV. Efficacy must not be compromised, including foaming, stain removal, hand feel, grease-cutting, etc.

Our approach involved examining various categories to comprehensively identify alternative preservatives for ECOS products. As an additional consideration, ECOS prefers that the alternative preservatives have a positive consumer perception. Based on these requirements, we explored food preservatives as simple solutions from the past that have already been regulated and used at a commercial scale. We also examined the EPA's list of safe chemical ingredients. Our research also extended to analyzing preservative systems used by other eco-friendly soap and detergent companies, as well as those employed in adjacent industries such as cosmetics and skincare. We investigated alternative production systems and delved into the chemical literature to discover preservation techniques that have not yet been widely adopted in the detergent industry. Lastly, we drew inspiration from ECOS' 2015 strategy list, in which they explored preservative alternatives. This approach was used to develop a list of possible preservatives that meet safety and environmental standards.

This approach was used to develop a list of possible preservatives. Throughout our search process, we were able to identify several classes of preservatives with varying pH ranges. However, further testing would be required to ensure these alternative preservatives can maintain product viscosity, ensure enzyme stability, and maintain the overall efficacy of the formulation.

Methods for Assessing Hazard Data

A comparative hazard assessment was conducted following the general approach developed by the GreenScreen for Safer Chemicals: Hazard Assessment Guidance (2018) to determine our hazard interpretations.[7] Authoritative listings, GreenScreen Assessments, and scientific literature from Google Scholar and Pharos-PubMed searches were reviewed. If hazard information was still lacking, safety data sheets (SDSs) were referenced. Hazards were categorized as very high, high, moderate, low, and very low, with high, moderate, and low confidence ratings. When our sources showed positive effects or no adverse health effects of an alternative, a low hazard was assigned. Hazards were determined to have low confidence if the only available information was from SDSs or PubChem, which often pulls information from SDSs because these hazards are often overstated to warn consumers about using the chemicals. Alternatives with contradicting evidence were also assigned a low confidence rating. Hazards with a high confidence rating had multiple studies with

consistent evidence or GreenScreen Assessments available. Alternatives with moderate confidence ratings fell in between.

In our hazard assessment, we focused on carcinogenicity/mutagenicity, skin sensitization, skin irritation, and eye irritation as the most relevant human health hazards. Exposure via inhalation and ingestion is less relevant, as products are not being used in an aerosolized form and should not be ingested. Environmental hazards, specifically acute and chronic aquatic toxicity and persistence/bioaccumulation must also be considered, as laundry detergents and soaps go down the drain.

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3. Carboxylic acids

Inspiration

Carboxylic acids have been used in food preservation for many years. Carboxylic acids that demonstrated antimicrobial properties were initially found in natural products like vinegar, citrus, or berries.[1] The prevalence of carboxylic acids in addition to their low toxicity, low cost, and high stability allowed them to be developed into a popular antimicrobial used by the food industry.[1,2] These carboxylic acids along with other weak organic acids are used to reduce the initial pathogenic load to ensure that it will be long lasting. This use is needed for ECOS products because their greatest concern is microbial contamination during the initial load of microbes rather than the development of microbes in finished products on the shelf or in the hands of consumers.

Overview

Carboxylic acids are a class of organic compounds where a carbon atom is bonded to an oxygen atom by a double bond and to a hydroxyl group (Figure 3.1). The fourth bond is linked to a hydrogen atom or another R group. This class of chemicals has intrinsic antimicrobial properties with the lipophilic structure that allows them to cross the plasma membrane by passive diffusion.[1] Within carboxylic acids, antimicrobial effectiveness varies depending on the pKa of the acid and the pH of the solution. After the carboxylic acid makes its way past the microbial plasma membrane, there is a dissociation of the acid leading to acidification within the cell.[1,3] This can result in changes to the activity of pH-sensitive enzymes, RNA and DNA synthesis, and cell wall assembly.[1] With the dissociation of the hydrogen from the hydroxyl group, the proton gradient used by cells is thrown off, negatively affecting the transporters and reducing nutrient intake into the cell. This process can also form reactive oxygen species damaging the membranes within the cell.[1] Carboxylic acids as a class function as antimicrobial agents, and sodium benzoate, potassium sorbate, and gluconolactone are examples of these acids that are already used in food production with demonstrated effectiveness (Table 3.1).

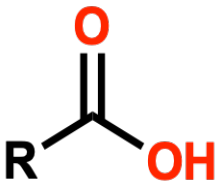
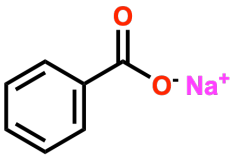
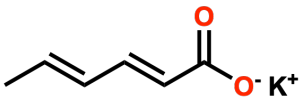
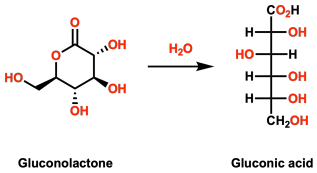


Figure 3.1. General chemical structure of a carboxylic acid.

Table 3.1. Chemical structures of sodium benzoate, potassium sorbate, gluconolactone, and gluconic acid.

Chemical Name	Sodium Benzoate	Potassium Sorbate	Gluconolactone and Gluconic Acid
CAS	532-32-1	24634-61-5	90-80-2
Structure			

Benzoic acid, the acid of sodium benzoate, was initially discovered in plants but not isolated until the 1500s.[4,5] For example, naturally occurring benzoic acid shows antimicrobial properties in cranberries, blackberries, mushrooms, and yogurt.[5] Despite this early discovery, it was only commercially available in the 1900s.[5] Since its synthesis, sodium benzoate has been added to many different food products. It was the first food preservative registered by the FDA in 1977.[6,7] Due to its low operating pH range, sodium benzoate is used mainly to preserve acidic products.[8]

Sorbic acid, the acid of potassium sorbate, was isolated from the berries of the mountain ash, or rowan, tree in 1859.[9,10] It is also found naturally in fennel and plums and is naturally synthesized during the fermentation of milk.[10] It is now chemically synthesized through a condensation reaction of a ketene and crotonaldehyde.[11] Potassium sorbate has been used in several food preservatives, including cheeses, meats, juices, ketchup, mayonnaise, and marmalade.[12,13,11] For meats, it is used as an alternative to nitrites to ensure shelf life.[9]

Gluconolactone, an oxidized derivative of glucose, is found widely in nature in both humans and bacteria.[14,15] Gluconic acid is the carboxylic acid that is formed when gluconolactone is hydrolyzed.[16] It is naturally synthesized in grapes, honey, and fruit juices.[14] It has been used as a food preservative in products such as tofu, wines, bread, cheese, and yogurt.[14] When exposed to water, gluconolactone hydrolyzes to gluconic acid, producing slow acting acidification that can have antimicrobial activity.[16]

Technical Performance

The concentration of carboxylic acids commonly used as preservatives ranges from 0.03-0.2%, depending on the formulation and pH.[17] The technical performance of carboxylic acids depends on the pH of the solution to which they are added (Figure 3.2).[18] Carboxylic acids need to retain the hydrogen atom that is attached to the oxygen in the hydroxyl group to retain its lipophilicity.[1] At higher pHs, the carboxylic acids will dissociate into their salts at a higher rate. This prevents the carboxylic acid from transporting across the microbial plasma membrane. Thus, carboxylic acids need a low pH to function as antimicrobials effectively.[19] Once the carboxylic acids are through the microbial membrane, they can dissociate, acidifying the cell and causing damage to proteins and the lipid membrane, leading to lysis and cell death.[1] Additionally, studies have found that carboxylic acids with shorter carbon chains have greater antimicrobial activity than those with longer carbon chains.[11] Their effectiveness as preservatives varies depending on their pKa and structure (Table 3.2). Sodium benzoate is the most potent antimicrobial with its low MIC values, even when compared to MIT. Gluconolactone, with its high MIC values, would need to be used at higher concentrations to be effective as a preservative.

Effect of pH on the Dissociation of Benzoic Acid

pH	Undissociated Acid (%)
3	93.5
4	59.3
5	12.8
6	1.44
7	0.144
pK	4.19

Figure 3.2. Increasing pH increases the amount of benzoic acid that is dissociated reducing its lipophilicity.

Table 3.2. MIC values of incumbents, sodium benzoate, potassium sorbate, and gluconolactone.

Chemical	MIC Value (µg/mL)				
	A. niger (Mold)	*C. albicans* (Yeast)	*E. coli* (Gram -)	*P. aeruginosa* (Gram -)	*S. aureus* (Gram +)
Phenoxyethanol[20]	1500	2000	2500	2500	3000
MIT	166[21]	0.5[22]	41[23]	15[22]	45[22]
Sodium benzoate[24]	*A. flavus* 50	2.5	5	5	10
Potassium sorbate[24]	*A. flavus* 50	50	5	10	10
Gluconolactone[25]	Data gap	Data gap	6300	3100	6300

≤100	>100	No effect	Data gap

Human & Environmental Health Performance

Carboxylic acids have a similar hazard profile to phenoxyethanol with some notable exceptions (Table 3.3). The hazard profile for carboxylic acids is also lower than that of MIT, providing a substantial improvement in skin irritation and aquatic acute and chronic toxicity, similar to the benefits provided by phenoxyethanol. Like MIT and phenoxyethanol, sodium benzoate, and potassium sorbate are considered a high hazard for eye irritation. Sodium benzoate also has a high hazard for skin sensitization, which is worse than phenoxyethanol. Potassium sorbate has moderate hazards for mutagenicity and aquatic acute and chronic toxicity. Gluconolactone has lower or similar hazards than MIT, phenoxyethanol, and the other carboxylic acids being considered.

Table 3.3. Hazard table for relevant endpoints of incumbents, sodium benzoate, potassium sorbate, and gluconolactone.

	Human Health Group I					**Human Health Group II**									**Environmental Health**		**Environmental Fate**		**Physical Hazards**	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[26]	**L**	**L**	L	**M**[27]	*L*	**M**	M	**L**	**M**	*L*	**L**	*L*[28]	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	**L**
MIT [29]	*L*[30]	**L**[31]	**L**	**L**[32]	DG	**vH**	M	DG	**L**	M	**H**[33]	*L*[34]	**vH**[35]	**vH**	**vH**	**vH**	*L*	vL	*L*	*L*
Sodium benzoate	*L*[27, 36]	**L**[37]	DG	*L*[6]	DG	*L*[38]	**L**[39]	**L**[40]	*L*[41]	*L*[41]	**H**[42]	*L*[38]	*L*[39]	**H**[38]	*L*[43]	DG	**L**[43]	**L**[43]	DG	**L**[44]
Potassium sorbate	**L**[36, 45]	*M*[12]	**L**[46]	**L**[46]	DG	**L**[47]	**L**[48]	**L**[48]	*L*[49]	*L*[49]	**L**[45]	**L**[45]	**L**[45]	**H**[50]	**M**[51]	**M**[51]	**vL**[51]	**vL**[50]	*L*[49]	**L**[49]
Gluconolactone[26]	*L*	*L*	*L*	**L**	DG	**L**	**L**	**L**	DG	DG	*L*	DG	*L*	*L*	**L**	*L*	**vL**	*vL*	*L*	**L**

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Remaining Questions

Enzymes are added to laundry detergents to improve the efficacy of stain removal. These enzymes are susceptible to denaturation in the low pH necessary for the functioning of carboxylic acids as preservatives. Is it possible to find enzymes that work at lower pHs that are necessary for the functioning of these carboxylic acids?

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4. Natural Alternatives

Inspiration

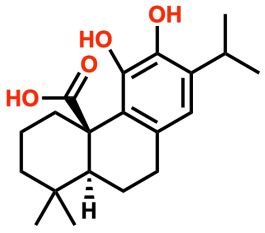
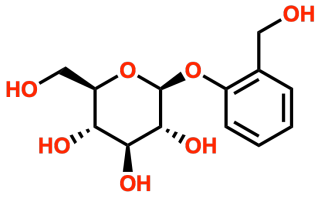
Our natural alternatives were inspired by plants that have developed defenses against microbes, pests, and environmental stress such as low water availability, high sun exposure, temperature fluctuations, and nutrient deprivation. Rosemary essential oil, which is derived from the leaves and flowery top of the rosemary plant, and willow bark extract, which is derived from the bark of the willow tree, are examples of these plants. Rosemary essential oil was explored due to its known antimicrobial properties, and inspiration for willow bark extract was drawn from the 2015 strategy list from ECOS. Thus, these natural alternatives were explored as preservatives in laundry detergents and soaps.

Overview

Essential oils have antimicrobial and antioxidant properties that allow them to extend the shelf life of food products.[1] In particular, rosemary essential oil has been an effective food preservative for yogurt-making.[2] The European Union has also approved rosemary extract as a food preservative after toxicity studies, confirming its safety for use in food products.[3] Willow bark extract is used as an antibacterial in personal care products.

Rosemary essential oil and willow bark extract are products from plants that contain phenolics, which provide some form of antimicrobial effect. Phenolic compounds can increase the permeability or destabilize the plasma membrane of microbes, which causes cell death or inhibition of extracellular enzymes.[4,5] Carnosic acid in rosemary essential oil and salicin in willow bark extract are some phenolics that contribute to their effectiveness as preservatives (Figure 4.1).

Figure 4.1. Chemical structures of carnosic acid and salicin.

Chemical Name	Carnosic Acid	Salicin
CAS	3650-09-7	138-52-3
Structure		

Although the mechanism of action for carnosic acid is not fully understood, it is thought that the lipophilic structures of these compounds allow for them to integrate into the bacterial membrane, allowing their hydrogen bond donor groups to interact with the phosphorylated groups to cause

membrane permeability.[6] One study demonstrates that the components of rosemary essential oil have a synergistic effect contributing to its broad spectrum antimicrobial efficacy.[7]

Salicin from willow bark extract is known for its effectiveness in treating pain, similar to aspirin, and it also functions as an antibacterial agent.[8] Salicin is a phenolic glycoside that forms salicylic acid when oxidized.[9] Similar to rosemary, the components of willow bark have synergistic properties that outpace the effect of any single ingredient.

Technical Performance

Based on current concentrations, rosemary essential oil is used from 0.5-0.7% in yogurt preservation.[2] Meanwhile, willow bark extract is commonly used as a preservative at concentrations of 2.5-5%.[10] Rosemary essential oil is active around a pH of 7.4,[11] while willow bark extract is active in the pH range of 3-7 based on the ECOS 2015 strategy list. Rosemary essential oil's components are synergistic and can prevent the growth of both bacteria and fungi. Rosemary essential oil is most effective against mold compared to yeast, gram-negative, and gram-positive bacteria. However, willow bark extract is only effective against bacteria and requires additional chemicals to combat yeast and mold (Table 4.1).

Table 4.1. MIC values of incumbents, rosemary essential oil, and willow bark extract.

Chemical	MIC Value (µg/mL)				
	A. niger **(Mold)**	***C. albicans*** **(Yeast)**	***E. coli*** **(Gram -)**	***P. aeruginosa*** **(Gram -)**	***S. aureus*** **(Gram +)**
Phenoxyethanol[12]	1500	2000	2500	2500	3000
MIT	166[13]	0.5[14]	41[24]	15[14]	45[14]
Rosemary essential oil	*A. flavus* 250[15]	5,000-10,000[16] (carnosol: 100)[17]	3,000-20,000[16,18]	1,000[16]	11,250[19] (carnosol: 32-256)[20]
Willow bark extract	Data gap	Data gap	None (salicylic acid: 4,000)[21]	Data gap SA: 500[22]	600-800[23] (salicylic acid: 4,000)[21]

≤100	>100	No effect	Data gap

In terms of the mechanism of action, rosemary oil contains several phenolic compounds and terpenoids that are responsible for its antimicrobial activity. Some representative compounds include α-pinene, β-pinene, 1,8-cineole, camphor, rosmarinic acid, carnosic acid, and carnosol. These compounds function largely via a membrane-disruption mechanism, where the hydrophobic groups embed into the bacterial cell wall membrane and affect its integrity.

As for willow bark, salicin—a precursor to salicylic acid—is one of the main antimicrobial compounds. Additionally, other phenolic compounds, such as triandrin, and flavonoids, such as (+)-catechin, are responsible for the antimicrobial effect of willow bark extract.[25] The primary mechanism of action is thought to involve bacterial cell wall disruption, but secondary mechanisms—such as enzyme inactivation from the metabolism of salicin and triandrin—are also plausible.[26,27]

A challenge with naturally sourced essential oils and extracts is batch-to-batch consistency. Depending on several factors such as the salinity of the soil, time of harvest, location of harvest, and oxidative stress of the environment, plants can have varied content of terpenes and phenolic compounds.[23] Additionally, the method of extraction or distillation can largely affect the distribution of active compounds that are extracted. These factors need to be rigorously tested to ensure that different batches of the desired extract or essential oil have similar MIC values against the microbes of interest.

Human & Environmental Health Performance

Both rosemary essential oil and willow bark extract have some lower hazards and data gaps than the incumbents (Table 4.2). Rosemary essential oil has a worse hazard for skin sensitization than phenoxyethanol. It has data gaps due to the high variability of the active compounds. Toxicity hazard assessment remains challenging and leaves several human, ecotoxicity, and physical hazard endpoints with data gaps.[28] Willow bark overall looks promising regarding its hazard profile, as it has a lower eye hazard than phenoxyethanol. It has similar carcinogenicity, skin sensitization, skin irritation, and aquatic acute toxicity hazards as phenoxyethanol. However, willow bark has data gaps for aquatic chronic toxicity and fate, which would require further investigation.

Table 4.2. Hazard table for relevant endpoints of incumbents, rosemary essential oil, and willow bark extract.

	Human Health Group I					**Human Health Group II**									**Environmental Health**		**Environmental Fate**		**Physical Hazards**	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[29]	**L**	**L**	L	**M**[30]	*L*	**M**	M	**L**	**M**	*L*	**L**	*L*[31]	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	**L**
MIT[32]	*L*[33]	**L**[34]	**L**	**L**[35]	DG	**vH**	M	DG	**L**	M	**H**[36]	*L*[37]	**vH**[38]	**vH**	**vH**	**vH**	*L*	vL	*L*	*L*
Rosemary Essential Oil	DG	*M*[39,40]	*H*[28]	*H*[28]	DG	**L**[28,41]	DG	**M**[42]	DG	DG	M[43]	DG	*L*[44]	DG	DG	DG	**L**[45]	DG	DG	DG
Willow Bark Extract	**L**[46,47]	**L**[23,47]	DG	DG	DG	**L**[23,47]	DG	DG	DG	**L**[48]	*L*[47]	DG	**L**[47,49]	*L*[47]	L[47]	DG	DG	DG	*L*[47]	*L*[47]

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Remaining Questions

Further research is required to understand if our proposed alternatives will work with the pH range specified by ECOS. A review of market cleaning products containing either rosemary essential oil or willow bark shows that many of these products are likely acidic in nature. To assess pH compatibility, a preservative efficacy test on prototypes containing these preservatives should be performed. Negative results on bacteria, fungi, and viruses would confirm literature findings of efficacy in basic pH solutions. Given that both rosemary essential oil and willow bark extract are naturally sourced, the active ingredient concentration may vary.

Additionally, the optimal concentration of either rosemary essential oil or willow bark extract in the final solution must be determined. For willow bark extract, it is also unknown which additional chemicals at which concentration work in combination to achieve the full antimicrobial effect. The associated health hazards for our relevant endpoints must be investigated as well.

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5. Peptides

Inspiration

Amino acids, the building blocks of life, combine as monomers to form peptides and proteins essential for structure, function, and homeostasis in living organisms. Among these critical functions, some peptides known as antimicrobial peptides (AMPs) serve as the first line of defense for organisms and can be effective against bacteria, fungi, viruses, and even cancer cells. AMPs are present in a wide range of organisms, ranging from humans to plants, and as of January 2024, almost 4000 antimicrobial peptides have been deposited into the antimicrobial peptide database.[1] While a primary focus of AMP research is targeted against antibiotic-resistant bacteria,[2,3] the use of AMPs as broad-spectrum preservatives for food and personal care products has also received interest. This section will highlight two candidate antimicrobial peptides, ε-poly-L-lysine (ε-PL) and nisin, but the field of antimicrobial peptides is rapidly growing, and AMPs will likely be more prevalent in the future.

Overview

Amino acids consist of a carbon backbone with four different groups bonded: an amino group, a carboxylic acid group, a side chain (R group), and a hydrogen atom. Peptides consist of short chains (2-50) of amino acids and are linked together by peptide bonds, which form from the condensation reaction of the amino group of one amino acid with the carboxyl group of the adjacent amino acid, as seen in Figure 5.1A. Peptides have a primary structure, described by their amino acid sequence, and sometimes a secondary structure, described by secondary interactions between their amino acid sequence that result in defined shapes such as α-helices and β-sheets. The function of peptides is closely tied to their structure, which is influenced heavily by the identity of the amino acid side chains. There are 20 genetically encoded amino acids that humans and other organisms incorporate into their proteins and peptides. These 20 amino acids differ by the side chain, which can be classified into several categories, as seen in Figure 5.1C. While peptides are typically linear, there are special cases that result in cyclic peptides in which the amino group of one amino acid forms a peptide bond with the carboxyl group of another amino acid on the other end of the chain, as illustrated in Figure 5.1B.

ε-poly-L-lysine (Table 5.1) is a homopeptide consisting of 25-30 lysine monomers where the side-chain amine, instead of the backbone amino group, is part of the peptide bond. It is produced biosynthetically through bacterial fermentation of a mutant *Streptomyces albulus* bacteria.[4–6] It is a water-soluble, thermally stable yellowish powder with a bitter taste. It has been widely used in the food preservation industry in products such as boiled noodles,[7] bread,[8] seafood,[9–11] fruits,[12–14] meats,[15–20], and cheese.[21] Nisin (Table 5.1) is a cyclic peptide produced by *Lactococcus lactis* bacteria as a bacteriocin or a peptide produced by a species of bacteria that is designed to kill other closely related or unrelated species of bacteria.[22,23] Given the prevalence of *L. lactis* in dairy

production, it is likely that humans have been consuming nisin for a very long time.[24] Nisin has been widely used to preserve dairy products,[25–30] meats,[31–37], and other food products.[38–42]

Figure 5.1 A. general structure of an amino acid and its reaction to form a peptide; **B.** comparison of linear and cyclic peptides; **C.** structures of the 20 canonical amino acids.

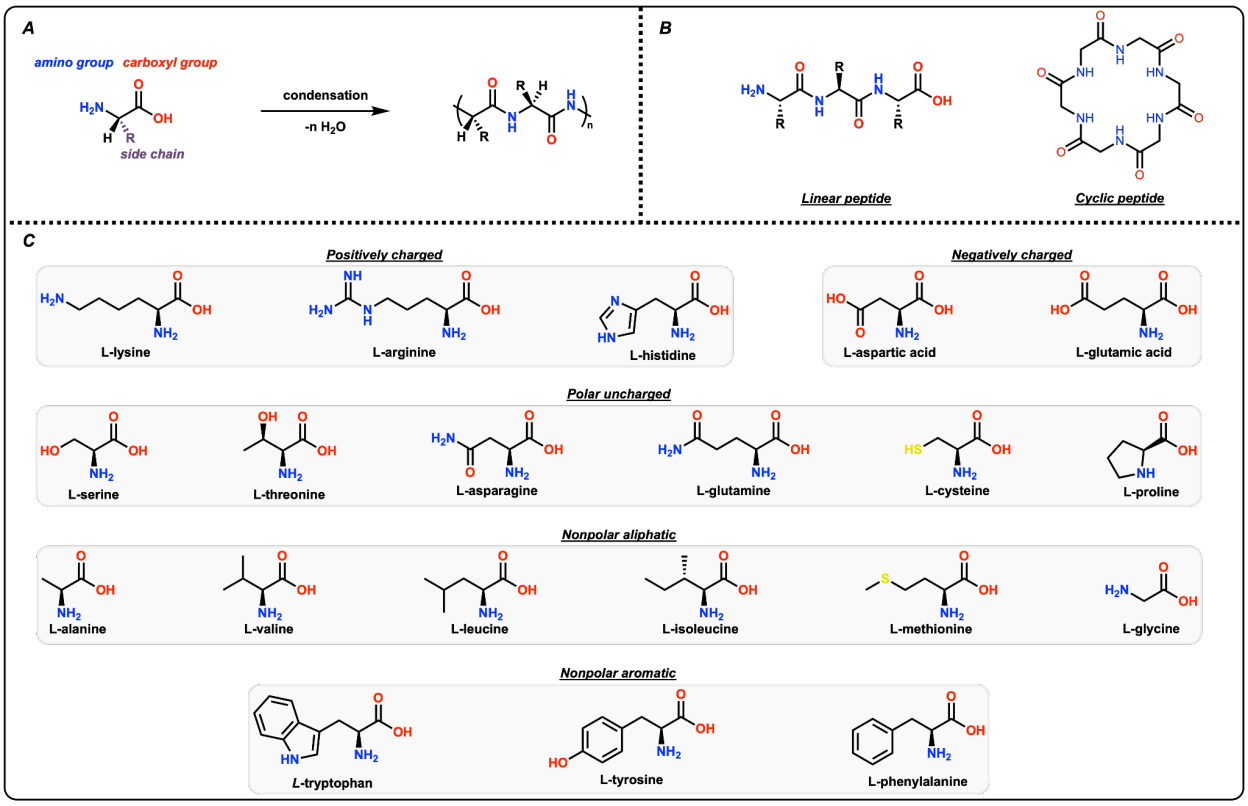
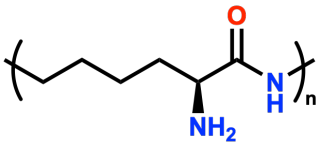
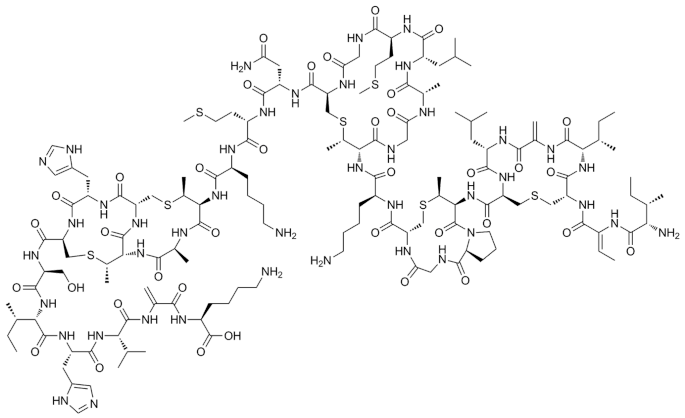


Table 5.1. Chemical structure of ε-PL and nisin.

Name	ε-poly-L-lysine	Nisin
CAS	28211-04-03	1414-45-5
Structure		

Technical Performance

The effective concentration of the peptides depends on factors such as the pH of the solution and the compatibility with other formula ingredients. AMPs typically contain positively charged side chains that are attracted to the negatively charged bacterial cell membranes, as well as hydrophobic side chains that allow for bacterial membrane disruption. AMPs interact with bacterial cell membranes, increasing their permeability and causing cell rupture and lysis. Additionally, cyclic peptides can sometimes cross the bacterial membrane and interfere with proteins and enzymes inside the cell.[3,43–45] The AMPs discussed in this section have a broad spectrum of activity, with their antibacterial activity being more potent than their antifungal activity. Table 5.2 summarizes MIC values for ε-PL and nisin. Both AMPs are approved for food use in the US, Japan, and China, with nisin also being approved in the EU.[46–51] ε-PL and nisin are approved for use in food products by the FDA in concentrations up to 0.025% (GRN000336 for ε-PL in various foods and GRN000065 for nisin in cheeses).

ε-PL is quite stable and highly soluble at pH values from 3 to 9 and retains its highest activity levels at pH values between 4 and 7.5.[52] The activity level of ε-PL can be affected by interacting with proteins in foods, such as egg albumin, but that is not a concern for personal cleaning products–with the exception of enzyme-based detergents in which compatibility will need to be tested. Its activity against *E. coli* manifests with ε-PL chain lengths of at least 9 lysines and improves with increased chain length up to 25-30 (commercially biosynthesized ε-PL).[53] Nisin is stable and highly soluble at low pH values, down to pH of 2, but is gradually less stable and soluble as the pH value rises up to alkaline pH values.[54] With that being said, the solubility of nisin at neutral pH values is still on the order of 1 mg/mL, which is higher than the approved use

concentration.[55] Regarding activity, nisin is about 5 times less effective at neutral pH compared to pH 3. As for stability, nisin experiences 40% decomposition after 120 days at room temperature and pH 6, as opposed to 20% decomposition at pH 3 and otherwise identical conditions. The activity retained after incubation is higher than can be explained by the remaining nisin, likely due to the residual antimicrobial activity of decomposed nisin.[55]

As seen in Table 5.2, both peptides are much more potent against bacteria than fungi. Nisin is most potent against gram-positive bacteria, with a high potency against gram-negative bacteria and a lower potency against fungi. ε-PL is generally potent against bacteria but is less potent against fungi as well. Nisin's MIC values can be improved if combined with a chelator such as EDTA.[60,61] This is due to improved membrane contact between nisin and the bacteria, which causes more efficient membrane disruption.

Table 5.2. MIC values of incumbents, ε-PL, and nisin.

Chemical	MIC Value (µg/mL)				
	***A. niger* (Mold)**	***C. albicans* (Yeast)**	***E. coli* (Gram -)**	***P. aeruginosa* (Gram -)**	***S. aureus* (Gram +)**
Phenoxyethanol[56]	1500	2000	2500	2500	3000
MIT	166[57]	0.5[58]	41[59]	15[58]	45[58]
ε-poly-L-lysine	250[52]	128-250[53,60]	1-12.5[53,61]	3-50[22,53]	4-12.5[53,61]
Nisin	*A. flavus* 250[62]	1-2[63]	12-16[64,65]	36-64[64,66]	2[66]

≤100	>100	No effect	Data gap

Human & Environmental Health Performance

Overall, peptides seem to have really safe hazard profiles that outperform the incumbent preservatives, as seen in Table 5.3 below. That said, much of this data has low confidence since it is derived from safety data sheets (SDS) and studies used for GRAS designation. Some notable data gaps are endocrine activity and aquatic toxicity, which are important since the products employing these preservatives will come into contact with skin and eventually be rinsed into the water supply. Persistence and bioaccumulation data gaps are not concerning since these peptides are made of amino acids that are prevalent in all organisms and are non-toxic.

Table 5.3. Hazard table for incumbents, ε-PL, nisin.

	Human Health Group I					**Human Health Group II**									**Environmental Health**		**Environmental Fate**		**Physical Hazards**	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[67]	**L**	**L**	L	**M**[68]	*L*	**M**	M	**L**	**M**	*L*	**L**	*L*[69]	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	*L*
MIT[70]	*L*[71]	**L**[72]	**L**	**L**[73]	DG	**vH**	M	DG	**L**	M	**H**[74]	*L*[75]	**vH**[76]	**vH**	**vH**	**vH**	*L*	vL	*L*	*L*
ε-poly-L-lysine	*L*[77]	*L*[78]	*L*[79]	*L*[80]	DG	**L**[78]	*L*[78]	*L*[78]	*L*[79]	DG	*L*[80]	*L*[80]	*L*[80]	*L*[80]	*L*[80]	*L*[80]	DG	DG	*L*[80]	*L*[80]
Nisin	*L*[81,82]	*L*[47]	*L*[47]	*L*[47]	DG	*L*[83]	*L*[83]	*L*[83]	DG	DG	*M*[84,85]	*L*[84]	*L*[84]	*L*[84]	DG	DG	DG	DG	*L*[84]	*L*[84]

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Remaining Questions

The main remaining question about using peptides as preservatives is their formulation compatibility. The performance of peptides as preservatives has been validated for food use, but there is no guarantee that the performance is unaffected in a detergent or soap formulation. Further testing will be required to ensure that peptides will not affect other aspects of the formulation, such as viscosity, hand feel, stain removal properties, etc. Additionally, enzyme-boosted detergent formulations may contain proteases and peptidases that could degrade the peptide preservatives. That said, ε-PL is condensed through the ε-amine of lysine, which gives it an unusual structure that might not be recognizable by the specific enzymes used in the formulation. Additionally, the peptides or the enzymes used could be improved using directed evolution approaches for better compatibility and stability. As for fungi, the MIC values of the peptides indicate only moderate activity, so it might be worth considering a blend of peptides and antifungal preservatives.

A very important remaining question is about the price and purity of peptide preservatives. Depending on the use levels, peptides may be a costly preservative replacement due to their biosynthesis via bacterial fermentation, which gives lower yields and throughput compared to chemical synthesis. Additionally, there are usually trace compounds from the bacterial cells used for the fermentation, and while these compounds are likely harmless, they could be potential allergens for people with dairy allergies.

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6. Hydroxamic Acids

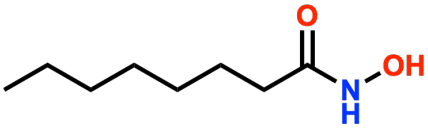
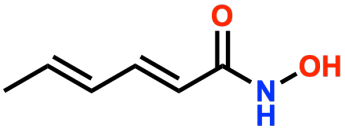
Inspiration

Exploration of hydroxamic acids as preservatives stems from their similarity to natural acids like caprylic and sorbic acids found in various oils and plants. Hydroxamic acids' ability to chelate metal ions and inhibit microbial growth is a property derived from their structural resemblance to natural siderophores.[1] Chelating refers to the ability of a molecule, such as hydroxamic acids, to form stable complexes with metal ions by binding to them through multiple coordination sites, effectively "grabbing" the metal like a claw. Siderophores are natural compounds produced by microorganisms to bind and transport metal ions, particularly iron, which they use to sustain growth in environments where metal availability is limited. These molecules, commonly found in microorganisms, efficiently scavenge essential metals from their environment, starving bacteria and fungi. Hydroxamic acids exhibit potent antimicrobial properties, making them a promising candidate for safer preservation. This dual functionality—antimicrobial efficacy and compatibility with natural biological systems—positions hydroxamic acid as an innovative and potentially sustainable solution to address the limitations of traditional chemical preservatives like Methylisothiazolinone (MIT) and Phenoxyethanol.

Overview

The functional group hydroxamic acids are organic compounds. These compounds are known for their metal-binding properties, which interfere with essential microbial processes, leading to effective preservation. They function as mild broad-spectrum antimicrobial agents.[1,2] The hydroxamic acids we will examine are capryl hydroxamic acid and sorbic hydroxamic acid, which can be synthesized from their corresponding carboxylic acids.

Figure 6.1. Chemical structures of capryl hydroxamic acid and sorbic hydroxamic acid.

Chemical Name	Capryl Hydroxamic Acid	Sorbic Hydroxamic Acid
CAS	7377-03-9	4076-62-4
Structure		

Technical Performance

Hydroxamic acids exhibit broad-spectrum antimicrobial activity against bacteria, fungi, and molds by chelating transition metals essential for microbial metabolism.[3] One study on hydroxamic acids suggests effective membrane disruption inhibits the growth of *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* at low concentrations, maintaining product integrity and shelf life.[4] The antimicrobial activity of hydroxamic acids is likely mediated through the inhibition of microbial urease, achieved via interaction with metal ions or reactions with sulfhydryl groups in enzymes.[5] Additionally, the effects of substituents suggest that both the formation of metal complexes and increased reactivity toward thiols play a significant role in enhancing their antimicrobial properties.

Hydroxamic acids are also resistant to degradation under varying pH levels from 4 to 8, ensuring reliable performance in diverse formulations. Capryl hydroxamic acids are commercially available and used as a preservative in 269 formulations (increased from 227 formulations reported in 2019) for cosmetics and household products such as soaps and detergents.[1,6] In 2020, The Expert Panel for Cosmetic Ingredient Safety at the Cosmetic Ingredient Review (CIR) assessed the safety of Capryl hydroxamic acid based on data from the FDA and cross-research from Australian and EU regulators.[1] The maximum leave-on and rinse-off concentrations of 0.25% in body and hand products and 0.3% in bath soaps and detergents. The published literature on Sorbic hydroxamic acid shows the minimum effective antimicrobial concentration is 0.1%.[2] However, data concerning the approved maximum concentration of sorbic hydroxamic acid were not found in published literature or regulatory agencies such as the FDA.

Table 6.1. MIC values of incumbents, capryl hydroxamic acid, and sorbic hydroxamic acid.

Chemical	MIC Value (µg/mL)				
	A. niger **(Mold)**	***C. albicans*** **(Yeast)**	***E. coli*** **(Gram -)**	***P. aeruginosa*** **(Gram -)**	***S. aureus*** **(Gram +)**
Phenoxyethanol[7]	1500	2000	2500	2500	3000
MIT	166[8]	0.5[9]	41[10]	15[9]	45[9]
Capryl hydroxamic acid [11]	*A. brasiliensis* 100	320	Data gap	1000	Data gap
Sorbic hydroxamic acid[2]	500	Data gap	Data gap	Data gap	Data gap

≤100	>100	No effect	Data gap

Human & Environmental Health Performance

Capryl hydroxamic acid has low skin sensitization (SnS), equivalent to phenoxyethanol; however, sorbic hydroxamic acid has high skin sensitization. Capryl hydroxamic acid has low human health

hazards, yet many data gaps remain that need further toxicity testing to understand its toxicological profile. However, capryl hydroxamic acid's environmental health endpoints remain high, especially aquatic toxicity.[12] Preliminary toxicological profiles align with stringent regulatory standards, such as those from the Cosmetic Regulations.[1] Sorbic hydroxamic acid has limited toxicity research.

Table 6.2. Hazard table for incumbents, capryl hydroxamic acid, sorbic hydroxamic acid.

	Human Health Group I					**Human Health Group II**									**Environmental Health**		**Environmental Fate**		**Physical Hazards**	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[13]	**L**	**L**	L	**M**[14]	*L*	**M**	M	**L**	**M**	*L*	**L**	*L*[15]	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	**L**
MIT [16]	*L*[17]	**L**[18]	**L**	**L**[19]	DG	**vH**	M	DG	**L**	M	**H**[20]	*L*[21]	**vH**[22]	**vH**	**vH**	**vH**	*L*	vL	*L*	*L*
Capryl hydroxamic acid[12]	DG	*L*[1,23]	DG	*L*	DG	*L*	DG	*M*	DG	*DG*	*L*[1]	DG	**L**	*H*[1]	*H*[5]	*H*	**vL**	*vL*	*L*	*L*
Sorbic hydroxamic acid	DG	DG	DG	DG	DG	*L*[24]	*M*[11]	DG	DG	DG	*H*[26]	DG	*H*[25,26]	*H*[25,26]	DG	DG	DG	DG	DG	DG

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Remaining Questions

Capryl hydroxamic acid and sorbic hydroxamic acids remain understudied in various aspects, including maximum safety concentration, efficacy, toxicity, viscosity, bioaccumulation, and degradation. How does hydroxamic acid perform in real-world conditions over an extended shelf life of 5-7 years? Are there degradation products, and do they impact efficacy or safety? Are there compatibility issues with specific product formulations, such as high-water-content products? How does it interact with other active ingredients commonly used in laundry detergents? What are the results of ecotoxicity testing for capryl hydroxamic acid and the fate endpoints for sorbic hydroxamic acid?

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7. Esters

Inspiration

In identifying possible alternatives to phenoxyethanol, our team looked at preservatives used in non-home care industries. Products in these industries sometimes use esters as preservatives. For instance, esters of p-hydroxybenzoic acid are used as a preservative in the foods, cosmetics, and pharmaceutical industries[1]. Given this versatility, the team wanted to investigate the potential application of other esters to ECOS's soaps and detergents. Products in other industries notably differ from liquid soaps and detergents in a few key ways, including formulation pH, state of matter, and exposure mechanism. Variations in product form, chemistry, and function across industries may be hurdles for a common application of ester preservatives. Given these caveats, the team identified sorbitan caprylate and propyl gallate as preservative options for ECOS soaps and detergents. An overview of the chemistry and technical performance and a hazard assessment follow.

Overview

Esters are formed during a chemical reaction called esterification, in which a carboxylic acid condenses with an alcohol to produce an ester and water. The combination of sorbitol and caprylic acid produces sorbitan caprylate and water[2]. Sorbitan caprylate is a particularly notable ester given the project objective because it can also act as a booster in a phenoxyethanol preservation system.[3,4] The analysis here focuses on sorbitan caprylate in isolation, but its combination with phenoxyethanol is worth further study, especially given that sorbitan caprylate has a lower hazard profile across the board with high confidence at multiple endpoints (Table 7.2). The reaction of gallic acid and propanol produces propyl gallate.[5] Propyl gallate is also found in nature via *Caesalpinea spinosa* pod extraction.[5]

Esters are often used in the food and pharmaceutical industries, although the type of ester employed varies depending on specific regulations and product chemistry. Sorbitan caprylate and propyl gallate are used in different industries. Sorbitan caprylate is used in the cosmetics industry as a surfactant and emulsifier but also comes with preservation-boosting properties.[2,6,7] On the other hand, propyl gallate is used in multiple industries. It is used in the foods and cosmetics industry as an antioxidant (classified as such by the FDA for foods) with downstream preservation via antimicrobial activity.[5,8,9] In addition, propyl gallate is used in the pesticide industry as an inert registered with the EPA.[10]

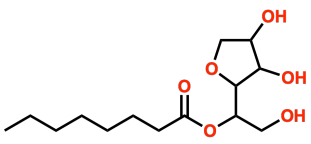
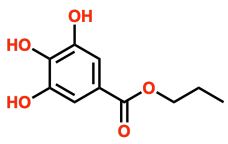
Esters and organic acids operate as antimicrobial agents in various ways depending on several factors, most notably the following: chain length, pKa/pH, hydrophobicity, and ability to chelate metals.[11] Chain length influences the passive cell membrane diffusivity; hydrophobicity influences the ability to dissolve within the cell membrane; chelating properties, meanwhile, sequester crucial

metal ions within a cell–rendering them unavailable.[11] Depending on the specific properties of an ester, one or multiple of these physical phenomena can disrupt intracellular biochemistry and ultimately result in cell death.[11]

Maximum concentration for both propyl gallate and sorbitan caprylate hinges on several factors, primarily industry-standard usage but occasionally through agency regulation. Propyl gallate is classified as a Generally Recognized As Safe (GRAS) substance by the FDA and–in accordance with antioxidation addition in foods detailed in 21 CFR 184.1660J–has a max total concentration of 0.02% of the fat or oil content.[8] The EPA considers propyl gallate as an inert when used in pesticide products and does not detail a maximum concentration.[10] In an EPA memorandum classifying propyl gallate as an inert, typical industry concentrations of propyl gallate in pesticide formulation are around 0.25%.[10] Lastly, in a 2007 review of 167 cosmetics products, the max concentration of propyl gallate was 0.1%.[12] Sorbitan caprylate does not tend to be used in foods and generally is not listed as an inert by the EPA. However, a 2014 review by The Cosmetics Ingredients List found that the max leave-on concentration of sorbitan caprylate was 1.5%, with a max rinse-off concentration of 1.0%.[13] Given the above, proposed starting concentrations for sorbitan caprylate and propyl gallate could be 1.5% and 0.25%, respectively.

Preservative efficacy generally varies according to formulation pH and individual chemical pKa values, both of which dictate the ratio of H^+ ions to undissociated acid ions in solution.[11] Propyl gallate, typically used as an antioxidant rather than a preservative, does not readily have optimum pH levels available but tends to be stable in neutral and mildly acidic environments, with some instability in mildly alkaline environments.[14] Parabens (esters of parahydroxybenzoic acid), which have two fewer hydroxyl groups attached to their benzene ring but otherwise similar in chemical structure to propyl gallate, have an optimum pH range of 4-8[15]–similar to the observed antimicrobial optimum pH in propyl gallate. Sorbitan caprylate does not seem to be sold as a standalone preservative but does exhibit broad-spectrum antimicrobial properties in combination with benzoic acid with a stable pH range of 4.0-6.5.[16] Additional sources indicate that other sorbitan caprylate-preservative combinations can be used in a pH range of 4-8.[4,16] Chemical structures for both chemicals are shown below in Figure 7.1.

Figure 7.1. Chemical structure of sorbitan caprylate and propyl gallate.

Chemical Name	Sorbitan caprylate	Propyl gallate
CAS	60177-36-8	121-79-9
Structure		

Technical Performance

Technical performance was evaluated using minimum inhibitory concentration (MIC) for each chemical against a set of benchmark organisms: *A. niger*, *C. albicans*, *E. coli (Gram negative)*, *P. aeruginosa (Gram negative)*, and *S. aureus (Gram positive)*. Cells were shaded in Table 7.1 below in yellow if the MIC was over 100 and green if below. MIT requires the lowest concentration for antimicrobial efficacy across the range of organisms considered, with propyl gallate and sorbitan caprylate demonstrating mixed performance against phenoxyethanol.

Table 7.1. MIC values for propyl gallate and sorbitan caprylate against benchmark microbes.

Chemical	MIC Value (µg/mL)				
	A. niger **(Mold)**	***C. albicans*** **(Yeast)**	***E. coli*** **(Gram -)**	***P. aeruginosa*** **(Gram -)**	***S. aureus*** **(Gram +)**
Phenoxyethanol[17]	1500	2000	2500	2500	3000
MIT	166[18]	0.5[19]	41[20]	15[19]	45[19]
Propyl gallate	A. brasiliensis 1000[21]	Data gap	1600[19]	3200[21]	1600[21]
Sorbitan caprylate	A. brasiliensis 100[21]	2500[22]	2500[22]	1000-2500[21,22]	2500[22]

≤100	>100	No effect	Data gap

Human & Environmental Health Performance

Looking at Table 7.2, Sorbitan caprylate had more data gaps than phenoxyethanol in a few key areas, such as endocrine activity, repeated systemic toxicity, and eye irritation. Generally, sorbitan caprylate had a lower hazard profile than phenoxyethanol across the board, with exceptions in acute chronic aquatic toxicity. As noted earlier in this section, phenoxyethanol and sorbitan caprylate can be combined; a packaged preservative combination could perhaps improve upon the hazard profile if both are used at lower concentrations than if used independently. Propyl gallate tended to have higher hazards than phenoxyethanol, with the exception of single neurotoxicity. However, phenoxyethanol is currently used in ECOS products at concentrations >0.7%, and – as noted earlier – propyl gallate is often used in pesticide products at concentrations of 0.25%. This lower concentration could potentially mitigate the overall hazard profile of the final product.

Table 7.2. Hazard data for sorbitan caprylate and propyl gallate.

	Human Health Group I					Human Health Group II									Environmental Health		Environmental Fate		Physical Hazards	
	C	M	R	D	E	AT	STS	STR	NS	NR	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[23]	**L**	**L**	*L*	**M**	*L*	**M**	*M*	**L**	**M**	*L*	**L**	*L*	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	**L**
MIT[24]	*L*	**L**	**L**	**L**	DG	**vH**	*M*	DG	**L**	*M*	**H**	*L*	**vH**	**vH**	**vH**	**vH**	*L*	*vL*	*L*	*L*
Sorbitan caprylate[21,25]	**L**	**L**	**L**	**L**	DG	**L**	**L**	DG	**L**	**L**	**L**	**L**	**L**	DG	**M**	**M**	**L**	**L**	*L*	**L**
Propyl gallate[21]	L	*L*	*L*	*L*	*H*	**M**	DG	DG	DG	DG	**H**	DG	**M**	vH	**vH**	**vH**	H	**L**	DG	DG

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Remaining Questions

This analysis demonstrates that there is some potential in using esters as alternatives to phenoxyethanol, particularly sorbitan caprylate, which has a similar technical performance (defined by MIC values for benchmark organisms) to phenoxyethanol and possibly a superior hazard profile - data gaps notwithstanding. However, key questions remain before either sorbitan caprylate or propyl gallate can be used in ECOS's soaps and detergents. First, while propyl gallate has a higher hazard profile than phenoxyethanol, its concentration in home care products (pesticides) tends to be lower than phenoxyethanol (soaps and detergents). A lower dose could mitigate against some of the high and very high hazards observed in both human health and environmental health hazard categories, but this would need to be verified. In addition, antimicrobial efficacy would need to be verified in the final formulas. MIC values are based on the raw material, so performance in a formula may be different. Antimicrobial efficacy results depend on preservative concentration, so preservative efficacy testing should be conducted with prototypes of varying levels of either sorbitan caprylate or propyl gallate, while the original formulas with phenoxyethanol can serve as a control. The results from the preservative efficacy tests (PET) should enable a decision on the final preservative concentration in the formula. Some of ECOS's products have a pH greater than 8, so these PET tests should incorporate a sensitivity analysis by including prototypes with pH values at the upper end of product specifications and perhaps a little higher to account for manufacturing variability. Successful PET results at the lower end of product pH specifications with failure elsewhere could suggest that these preservative alternatives function better at lower pH values and may open up the possibility of reformulating the product chassis to reflect a lower pH specification. Lastly, evaluations such as hard surface cleaning tests, rheometer measurements, and consumer testing for hand feel should be performed to validate prototype parity with the original phenoxyethanol based ECOS products.

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8. Polyols

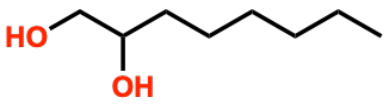
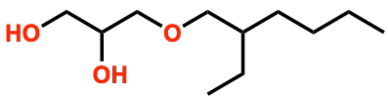
Inspiration

Polyols present a promising replacement for use as preservatives in cleaning products such as laundry detergents, hand soap, and dish soap because of the main necessity of reducing water activity in product [1]. Since water is an essential factor for microorganisms to grow, polyols have shown promising results in minimizing water activity.[2] A study investigated various binary systems, including synthetic glycerin, natural glycerin, and synthetic and natural butan-1,3-diol, all at a concentration of 4 wt%. The researchers hypothesized that adding the polyol drop by drop increased the contact interface between water and polyol, enhancing their interactions and reducing water activity. This reduction in water activity can significantly inhibit microbial growth, making polyols an effective preservative option in cleaning products.[3] Based on this understanding, it is worth noting that ECOS has already been using polyol-based preservatives in their products. Specifically, they use ethylhexylglycerin and caprylyl glycol as preservative boosters in combination with phenoxyethanol. However, we aim to show and investigate that these polyols can effectively function as the main preservative for their products.

Overview

Polyols, known as diols or glycols, depending on the number of hydroxyl groups (-OH) in their structure,[4] are versatile compounds widely used in cosmetics and personal care products. Compounds with two hydroxyl groups are referred to as diols, while those with two or more are classified as polyols. Among these, caprylyl glycol and ethylhexylglycerin (Figure 8.1) have gained significant attention for their multifunctional properties and use as preservative boosters.

Figure 8.1. Chemical structure of caprylyl glycol and ethylhexylglycerin.

Chemical Name	Caprylyl glycol	Ethylhexylglycerin
CAS	1117-86-8	70445-33-9
Structure		

Caprylyl glycol,[5] also known as 1,2-octanediol, is a medium-chain diol with strong antimicrobial properties, is a colorless liquid or semi-solid derived from raw natural materials that are a fatty acid naturally found in coconut oil, palm oil, and milk of some mammals.[6] It is commonly used in cosmetics to restrict bacterial growth and boost the efficacy of traditional preservatives. Additionally, caprylyl glycol is a humectant and emollient, retaining hydration and improving the skin feel of formulations. It is often combined with other preservatives like phenoxyethanol to

create synergistic effects, allowing for lower concentrations of each preservative while maintaining broad-spectrum protection.[7]

Ethylhexylglycerin,[8] also known as 3-[(2-ethylhexyl)oxy]-1,2-propanediol, is a colorless liquid derived from plant sources such as palm or soy. It is a multifunctional ingredient that acts as an emollient, surfactant,[9] and preservative booster in cosmetics and household products. Ethylhexylglycerin is particularly valued for its ability to enhance the efficacy of other preservatives, allowing formulators to use lower concentrations of traditional preservatives while maintaining product stability and safety.[10] It also has mild antimicrobial properties of its own, helping to protect products against bacteria and fungi.[10] Additionally, its emollient properties contribute to the smooth feel of products on the skin, making it a versatile ingredient in the cosmetics industry. However, it's important to note that while generally considered safe for use in cosmetics when adequately formulated, there have been some reported cases of allergic contact dermatitis associated with ethylhexylglycerin in certain individuals.[11]

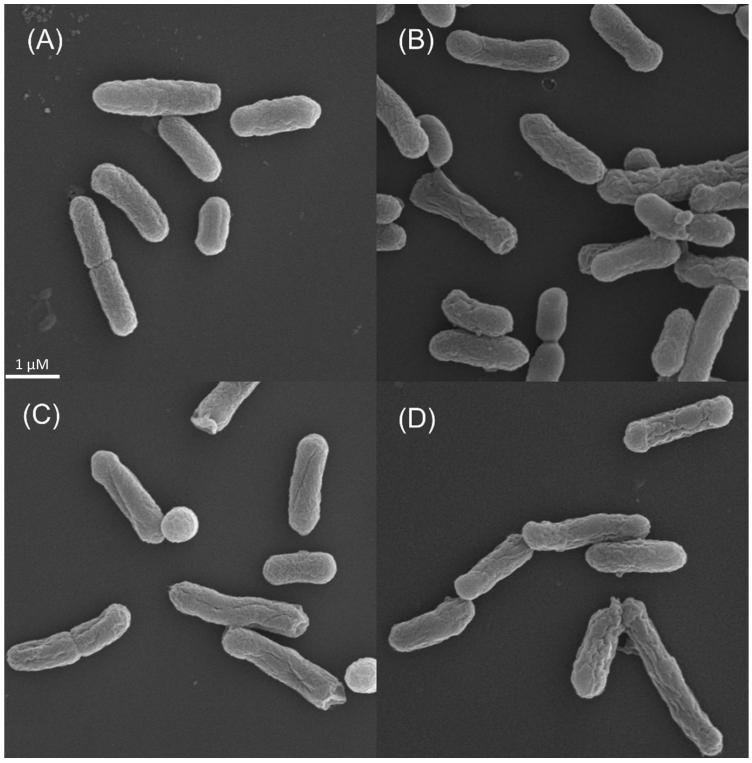
Technical Performance

Caprylyl glycol is usually used as a booster of 0.5% or lower concentrations. Some studies indicated that it is effective against various microorganisms, including bacteria (*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*), yeast (*Candida albicans*), and mold (*Aspergillus niger*).[10] Also, a research study showed that caprylyl glycol can cause some irritations when used as a preservative in cosmetic formulations at concentrations higher than 0.5%.[12] Caprylyl glycol is effective over a wide pH range. While finding a trustworthy reference was impossible, we can consider that laundry detergent companies like ECOS have used this preservative as a booster in a pH range of 6-8.5 when combined with phenoxyethanol. Caprylyl glycol is a C-8 aliphatic 1,2 diol that breaks down and disrupts microbial cell membranes, interfering with the integrity of microbial cell membranes and effectively disrupting their function.[12,13]

Ethylhexylglycerin, when combined with phenoxyethanol works better in a wide pH range of 6-9 in ECOS hand and dish soap products. It is usually used as a booster in lower concentrations of less than 0.5%. It also has limited solubility in water, approximately 0.1%, making it only slightly soluble. However, it is highly soluble in organic solvents, including alcohols, glycols, and glycol ethers.[14] When used as a preservative, it helps to destroy the bacterial cell membrane by reducing the surface tension on the cell wall. With this, they will prevent the bacteria from growing.[9] A study investigated the effects of cleaning chemicals on non-growing bacteria, focusing on a combination of phenoxyethanol and ethylhexylglycerin over a 24-hour period and the same results of the preservatives independently. These treatments were extremely effective, killing more than 99.9% of the bacteria. Researchers observed significant changes in the appearance of the bacteria compared to untreated bacteria the treated bacteria had rough surfaces (Figure 8.2). This experiment shows that these preservatives kill bacteria effectively by severely damaging their

surface structure, causing visible deformities.[9] One important observation from this research is that ethylhexylglycerin was used alone in a low concentration of 0.125% and resulted in a higher impact on the surface structure of the bacteria. Evidence to support the use of ethylhexylglycerin as a preservative independent of phenoxyethanol.

Figure 8.2. Electron microscopy scans of cells showing (A) Untreated control in Sodium phosphate buffer; (B) 0.75% (0.675% phenoxyethanol + 0.075% ethylhexylglycerin); (C) 1.125% phenoxyethanol; (D) 0.125% ethylhexylglycerin.[9]



When comparing MIC values of phenoxyethanol, ethylhexylglycerin, and caprylyl glycol, we can observe that their antimicrobial efficacy is generally similar across different microorganisms.[15] These MIC values (Table 8.1) indicate that all three compounds have >100 antimicrobial activity, with slight variations in effectiveness against different microorganisms ethylhexylglycerin and caprylyl glycol show slightly lower MIC values for some microorganisms compared to phenoxyethanol, suggesting they may be potent in certain cases. Given this performance, we see the potential of these two preservatives as the primary option; however, more studies need to be conducted to support this theory.

Table 8.1. MIC values of incumbents, ethylhexylglycerin and caprylyl glycol.

Chemical	MIC Value (µg/mL)				
	A. niger **(Mold)**	***C. albicans*** **(Yeast)**	***E. coli*** **(Gram -)**	***P. aeruginosa*** **(Gram -**	***S. aureus*** **(Gram +)**
Phenoxyethanol[15]	1500	2000	2500	2500	3000
MIT	166[16]	0.5[17]	41[18]	15[17]	45[17]
Ethylhexylglycerin[15]	1500	1500	1500	2000	1500
Caprylyl glycol[15]	1000	2000	1000	2000	2000

≤100	>100	No effect	Data gap

Human & Environmental Health Performance

In summary, our alternatives exhibit lower or comparable hazards compared to MIT (Table 8.2). When comparing caprylyl glycol and ethylhexylglycerin with phenoxyethanol, all three are classified as low hazard in almost all Group I for human health, differing mainly in their confidence levels. In Group II, caprylyl glycol and phenoxyethanol share a similar profile, both showing high potential for eye irritation (IrE). In contrast, ethylhexylglycerin has a moderate hazard for skin sensitization (SnS) and a very high hazard for eye irritation (IrE) compared to MIT. Regarding environmental health, caprylyl glycol performs better than MIT, ethylhexylglycerin outperforms caprylyl glycol, and phenoxyethanol has the most favorable profile with lower hazards. Finally, in the Fate (F) assessment, both MIT and phenoxyethanol, along with caprylyl glycol, demonstrate very low toxicity, while ethylhexylglycerin shows moderate hazard. Overall, polyols present a hazard profile that is more concerning than phenoxyethanol but better than MIT's.

Table 8.2. Hazard table for relevant endpoints of incumbents, ethylhexylglycerin and caprylyl glycol.

	Human Health Group I					Human Health Group II									Environmental Health		Environmental Fate		Physical Hazards	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[19]	**L**	**L**	L	**M**[20]	*L*	**M**	M	**L**	**M**	*L*	**L**	*L*[21]	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	**L**
MIT[22]	*L*[23]	**L**[24]	**L**	**L**[25]	DG	**vH**	M	DG	**L**	M	**H**[26]	*L*[27]	**vH**[28]	**vH**	**vH**	**vH**	*L*	vL	*L*	*L*
Ethylhexylglycerin[19]	*L*	*L*	*M*	*L*	DG	**M**	**M**	*M*	*L*[29]	*L*	M	DG	**L**	**vH**	**M**	**M**	*M*	**vL**	*L*	**L**
Caprylyl glycol[19]	*L*	**L**	*L*	**L**	*L*[7]	**L**	*L*[7]	**L**	**M**	**L**	**L**	DG	**L**	**H**	*H*	*M*	**vL**	**vL**	*L*	**L**

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Remaining Questions

What percentage should these alternatives be used, and how effective are they without being used as boosters? How much can the preservatives used as the primary ones interfere with the product's viscosity? Additionally, factors such as the low solubility of ethylhexylglycerin can impact the product's overall performance, including foaming, stain removal, hand feel, grease-cutting, and more.

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9. Phenyl Alkyl Alcohols

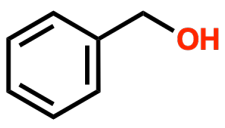
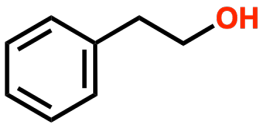
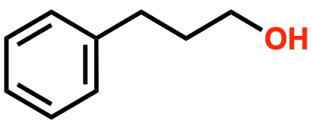
Inspiration

Phenyl alkyl alcohols are common preservatives in cosmetics, skincare products, detergents, soaps, pharmaceuticals, and food products. They are found in plant extracts, fruits, and wine but are chemically synthesized for mass use.[1] Inspiration was drawn from the 2015 strategy list from ECOS, in which preservative blends containing benzyl alcohol and phenethyl alcohol were explored. In these blends, benzyl alcohol or phenethyl alcohol were combined with other compounds, including dehydroacetic acid, benzoic acid, sorbic acid, caprylyl glycol, potassium sorbate, sodium benzoate, and glycerin, to boost its effects. In particular, phenoxyethanol and benzyl alcohol are the most commonly used phenol preservatives and have similar antimicrobial mechanisms of action.[2] Benzyl alcohol has been well-studied for its efficacy as a preservative and its health effects. In addition to benzyl alcohol, phenethyl alcohol and phenylpropanol were explored as alternatives to phenoxyethanol. Phenyl alkyl alcohols also have a floral scent that is often used for fragrance in formulations, but they could be beneficial as both a preservative and fragrance for specific types of ECOS-scented products.

Overview

Phenyl alkyl alcohols belong to a class of aromatic alcohols, where a phenyl group (benzene ring) is attached to an alkyl group (chain of carbon atoms), which is then connected to a hydroxyl group (-OH) (Figure 9.1). Benzyl alcohol, phenethyl alcohol, and phenylpropanol are colorless liquids with multiple purposes, including as preservatives, solvents, or fragrances due to their antimicrobial, physical, and aromatic properties.[3] The main difference between the three is the number of carbons in the chain.

Figure 9.1. Chemical structures of benzyl alcohol, phenethyl alcohol, and phenylpropanol.

Chemical Name	Benzyl Alcohol	Phenethyl Alcohol	Phenylpropanol
CAS	100-51-6	60-12-8	122-97-4
Carbon Chain Length	1	2	3
Structure			

Benzyl alcohol is a type of phenyl alkyl alcohol with a short alkyl chain and consists of a benzene ring attached to a methanol group.[4] It is a colorless, aromatic liquid and has both hydrophilic and lipophilic properties due to the presence of both a hydroxyl group and an aromatic ring. These

properties allow benzyl alcohol to dissolve in both water and organic solvents, making it highly useful.[4] It naturally occurs in apricots, cocoa, snap beans, cranberries, and in the essential oil of many plants, including jasmine, hyacinth and ylang-ylang, but it is industrially produced through the hydrolysis of benzyl chloride.[5]

Phenethyl alcohol is essentially the same as phenyl alkyl alcohol, except the alkyl chain is an ethyl group of two carbon atoms attached to the phenyl ring. Similar to benzyl alcohol, phenethyl alcohol is a colorless liquid with a pleasant floral odor.[6] Phenethyl alcohol naturally occurs in various flowers, including rose, hyacinth, and geranium, but it is usually chemically synthesized for mass production and use.[1]

Phenylpropanol has one carbon longer chain between the primary alcohol and aromatic moiety compared to benzyl alcohol and phenethyl alcohol.[7] It looks colorless to very pale yellow, slightly oily, and slightly viscous, and it has a faint floral hyacinth-mignonette odor.[7] Phenylpropanol can be found naturally in hyacinths, narcissus, and ripe strawberries, but it is also often chemically synthesized.

Technical Performance

The concentration of phenyl alkyl alcohols as a preservative typically ranges from 0.3-2.5%, depending on the formulation and pH. Benzyl alcohol, phenethyl alcohol, and phenylpropanol are generally active in the pH range from 3-10, but they are more effective preservatives in acidic conditions. Phenyl alkyl alcohols act as an antimicrobial due to their lipophilic properties that allow them to disrupt the structure of cell membranes of microorganisms.[2] They cause rapid denaturation of proteins, leading to cell lysis and death.[4,8] Their effectiveness against different types of bacteria, yeasts, and mold varies (Table 9.1). Benzyl alcohol is the most potent antimicrobial compared to the other alcohols given its low MIC values. Phenethyl alcohol is needed at a higher concentration to be effective. Phenylpropanol has several data gaps regarding its antimicrobial performance.

Table 9.1. MIC values of incumbents, benzyl alcohol, phenethyl alcohol, and phenylpropanol.

Chemical	MIC Value (µg/mL)				
	A. niger **(Mold)**	***C. albicans*** **(Yeast)**	***E. coli*** **(Gram -)**	***P. aeruginosa*** **(Gram -)**	***S. aureus*** **(Gram +)**
Phenoxyethanol[9]	1500	2000	2500	2500	3000
MIT	166[10]	0.5[11]	41[12]	15[11]	45[11]
Benzyl alcohol[13]	46.2	23.1	1.5	18.5	0.1
Phenethyl alcohol	*A. flavus* 1000[14]	800-3,200[15]	1,800[16]	4,600[17]	5,000[17]
Phenylpropanol[18]	*A. brasiliensis* 1000	Data gap	Data gap	10,000	Data gap

≤100	>100	No effect	Data gap

Benzyl Alcohol

Benzyl alcohol is active over a broad pH range of 3 to 8.5, but it is most effective below a pH of 7.[19] For example, benzyl alcohol's decimal reduction time (D-value) for *A. niger* is 28.8 at a pH of 5, and the D-value is 76.8 at a pH of 6. The D-value indicates a microorganism's resistance to the preservative, with a smaller D-value meaning a more effective preservative. The maximum allowable concentration of benzyl alcohol is 1.0%.[20] It is most active against gram-positive bacteria and moderately active against gram-negative bacteria, yeast, and molds.[20,21]

It is important to consider the material of the product containers, as certain preservatives may not be compatible with all materials. Benzyl alcohol is incompatible with methylcellulose and can be absorbed by the rubber enclosures used in drug containers. It can also slowly be absorbed by enclosures made of natural rubber, neoprene, and butyl rubber. If rubber containers are used, they should be coated with fluorinated polymers. Plastic containers are also not recommended unless they are polypropylene containers or coated with fluorinated polymers.[22]

Phenethyl Alcohol

Phenethyl alcohol is generally stable in the pH range of 4 to 8. When it was tested at concentrations of 0.3%, 1%, and 2.5% in cosmetic formulations (emulsion, cleansing, and hair conditioner), there were hardly any changes in the physical appearance of the formulations.[23] The only exception was that 2.5% of phenethyl alcohol in the cleansing solution reduced foam formation.

Phenethyl alcohol causes a rapid and reversible breakdown in the permeability barriers of bacterial cells. It affects the function of intracellular organs and inhibits DNA synthesis in *E. coli* but not RNA and protein synthesis.[23,24] It permeabilizes gram-negative cell envelopes, and for gram-positive bacteria, the plasmic membrane in *S. aureus* is solubilized.[25] There are correlations

between the alterations in the structural integrity of the cytoplasmic membrane in gram-negative cells and the loss of cell viability. However, it cannot be inferred that this membrane damage is the only cause of this lethal effect.[25]

Phenethyl alcohol exhibited strong antimicrobial activity to *C. albican*s, *P. aeruginosa*, *S. aureus*, and *E. coli*.[23] In emulsion and cleansing solutions, the minimum required concentration of phenethyl alcohol was 1.0% at any tested pH range. In conditioner formulations, the minimum required concentration of phenethyl alcohol was 2.5% for a pH of 4 to 6, as a concentration of 1.0% may facilitate microbial growth.[23]

Phenylpropanol

Phenylpropanol can be used with caprylyl glycol as a preservative in the pH range of 3 to 10. It is typically used in concentrations of up to 0.3% as a preservative.[26] Like benzyl and phenethyl alcohol, phenylpropanol acts as an antimicrobial by disrupting cell membranes, which damages their cell structure and causes cell death. It has strong activity against bacteria and fungi.

Based on various health endpoints, the maximum acceptable concentration of phenylpropanol added as a fragrance in finished products is 4.9% for rinse-off products with body and hand exposure (e.g. soap) and 6.2% for household care products with mostly hand contact (e.g. hand dishwashing detergent).[7] There is no restriction on the maximum acceptable concentration in other care products that are not intended for direct skin contact or have minimal or insignificant transfer to the skin.[7]

Human & Environmental Health Performance

Overall, our alternatives have lower or similar hazards compared to MIT, and benzyl alcohol has the most similar hazard profile to phenoxyethanol except for skin sensitization (Table 9.2). Hazard information for benzyl alcohol is rated with high confidence due to strong evidence and its 2019 Greenscreen Assessment. It received a benchmark rating of 2 from this assessment, which means "use but search for safer alternatives."[20] Furthermore, phenethyl alcohol may be a good alternative based on its hazards, as it has a lower hazard for eye irritation than the incumbents. Even with a moderate eye irritation hazard, ocular exposure is less relevant for ECOS products. Phenethyl alcohol's higher hazard for aquatic acute toxicity compared to phenoxyethanol may be concerning, but further data is needed. Finally, phenylpropanol's hazards for skin sensitization, skin irritation, eye irritation, and aquatic acute toxicity are higher compared to phenoxyethanol. Given benzyl alcohol and phenethyl alcohol's hazards and data availability, these two alcohols appear to be the safest within this strategy.

Table 9.2. Hazard table for relevant endpoints of incumbents, benzyl alcohol, phenethyl alcohol, and phenylpropanol.

	Human Health Group I					**Human Health Group II**									**Environmental Health**		**Environmental Fate**		**Physical Hazards**	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[20]	**L**	**L**	L	**M**[27]	*L*	**M**	M	**L**	**M**	*L*	**L**	*L*[28]	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	**L**
MIT[29]	*L*[30]	**L**[31]	**L**	**L**[32]	DG	**vH**	M	DG	**L**	M	**H**[33]	*L*[34]	**vH**[35]	**vH**	**vH**	**vH**	*L*	vL	*L*	*L*
Benzyl alcohol	**L**[20,36]	**L**[20]	**L**[20]	*M*[20]	DG	**M**[13,20]	DG	**L**[20]	*M*[20]	*H*[20]	**H**[20]	*L*[3,20,37]	**L**[20]	**H**[20]	**L**[20]	**L**[20]	**vL**[20]	**vL**[20]	*L*[20]	**L**[20]
Phenethyl alcohol	DG	**L**[28,38]	*M*[38,39]	*M*[28,38,40]	DG	*M*[6,39]	*M*[39]	**L**[28]	*M*[41]	*M*[41]	**L**[6,28]	*L*[28,41]	**L**[6]	*M*[6,38]	*M*[28]	DG	*L*[28]	*L*[28]	DG	DG
Phenylpropanol	DG	**L**[7]	L[7]	DG	*L*[42]	*vH*[42]	DG	*H*[7]	DG	DG	M[7,43]	DG	*M*[42,43]	*vH*[42]	**M**[7]	DG	**L**[7]	**L**[7]	*L*[42]	DG

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate confidence	*Low confidence*

Remaining Questions

At what percentage should these alternatives be used in ECOS' formulations? Given that phenyl alkyl alcohols are less effective in the more acidic conditions of ECOS products, what kinds of boosters or other preservatives would be used in combination? What are the human and environmental health hazards of those combinations? Lastly, would the floral scent of phenyl alkyl alcohols be a significant issue, or could ECOS use this opportunity specifically for floral-scented products?

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10. Technical Performance

Table 10.1 contains the MIC values for our preservatives against the following microbes: *Aspergillus niger* (mold; if no values found for *A. niger*, then other *Aspergillus* species are substituted), *Candida albicans* (yeast), *Escherichia coli* (gram negative bacteria), *Pseudomonas aeruginosa* (gram negative bacteria, industrially-relevant pathogen of concern), and *Staphylococcus aureus* (gram positive bacteria).

While a lower MIC value is usually desirable, it is important to note that lower MIC values don't always mean that a specific preservative is better. MIC values have to be considered in context of the final formulation concentration, which takes into account the hazards of the preservative. In order to have a comparison where both potency and safety are considered, we used a measure called the preservative Safety Index (SI), which is defined by the formula below:

$$Safety\ Index\ = \frac{concentration\ in\ final\ formulation}{minimum\ inhibitory\ concentration}$$

This formula is similar to that of the therapeutic index[1], which is the ratio of the maximum safe dose of a drug to its minimum effective dose. In the case of SI, higher values indicate that there is a wider margin between the concentration that is safe to use in a formulation and the concentration needed for the preservative to be effective against a specific microbe. Figures 10.1-10.5 show plots of the safety indices of our proposed preservatives against different microbes, normalized to that of phenoxyethanol. These plots are symmetric log functions, allowing for convenient visualization of both positive and negative data values. A value of 1 indicates that a preservative has an SI 10 times higher than phenoxyethanol, while a value of 2 indicates that the preservative has an SI that is 100 times higher than phenoxyethanol.

Table 10.1. MIC values against select microorganisms for all chemicals discussed in report.

Chemical	MIC Value (µg/mL)				
	***A. niger* (Mold)**	***C. albicans* (Yeast)**	***E. coli* (Gram -)**	***P. aeruginosa* (Gram -)**	***S. aureus* (Gram +)**
Phenoxyethanol[2]	1500	2000	2500	2500	3000
MIT	166[3]	0.5[4]	41[5]	15[4]	45[4]
Sodium benzoate[6]	*A. flavus* 50	2.5	5	5	10
Potassium sorbate[6]	*A. flavus* 50	50	5	10	10
Gluconolactone[7]	Data gap	Data gap	6300	3100	6300
Rosemary essential oil	*A. flavus* 250[8]	5,000-10,000[9] (carnosol: 100[10])	3,000-20,000[9,11]	1,000[9]	11,250[12] (carnosol: 32-256)[13]
Willow bark extract	Data gap	Data gap	None (SA: 4,000)[14]	Data gap SA: 500 [15]	600-800[16] (SA: 4,000)[14]
ε-poly-L-lysine	250[17]	128-250[18,19]	1-12.5[18,20]	3-50[18,21]	4-12.5[18,20]
Nisin	*A. flavus* 250[22]	1-2[23]	12-16[24,25]	36-64[24,26]	2[26]
Capryl hydroxamic acid[27]	*A. brasiliensis* 100	320	Data gap	1000	Data gap
Sorbic hydroxamic acid[28]	500	Data gap	Data gap	Data gap	Data gap
Propyl gallate	A. brasiliensis 1000[29]	Data gap	1600[19]	3200[29]	1600[29]
Sorbitan caprylate	A. brasiliensis 100[29]	2500[30]	2500[30]	1000-2500[29,30]	2500[30]
Ethylhexylglycerin[2]	1500	1500	1500	2000	1500
Caprylyl glycol[2]	1000	2000	1000	2000	2000
Benzyl alcohol[31]	46.2	23.1	1.5	18.5	0.1
Phenethyl alcohol	*A. flavus* 1000[32]	800-3,200[33]	1,800[34]	4,600[35]	5,000[35]
Phenylpropanol[36]	*A. brasiliensis* 1000	Data gap	Data gap	10,000	Data gap

≤100	>100	No effect	Data gap

Figure 10.1. Preservative safety index against *Aspergillus spp.* for all chemicals.

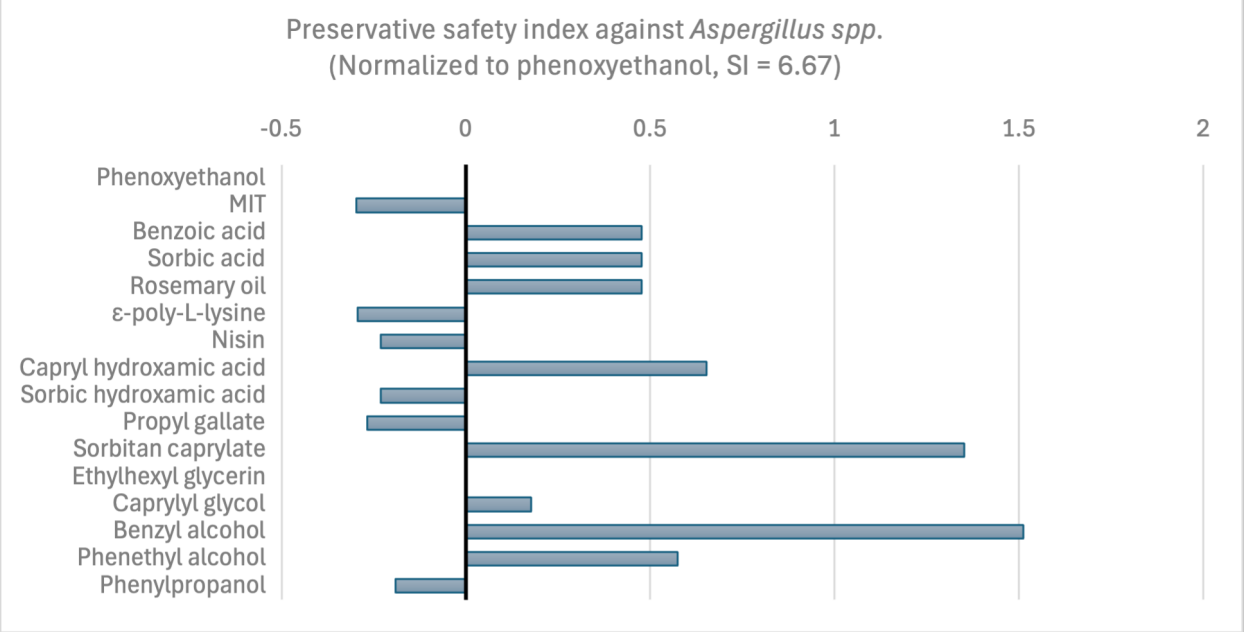


Figure 10.2. Preservative safety index against *Candida albicans* for all chemicals.

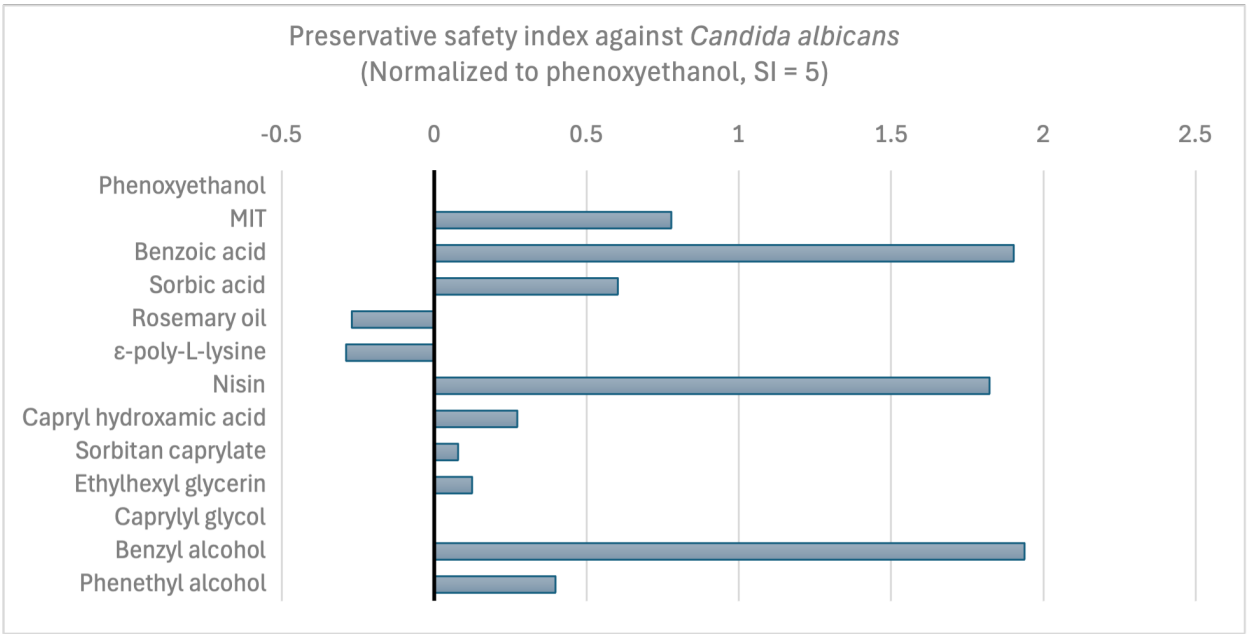


Figure 10.3. Preservative safety index against *Escherichia coli* for all chemicals.

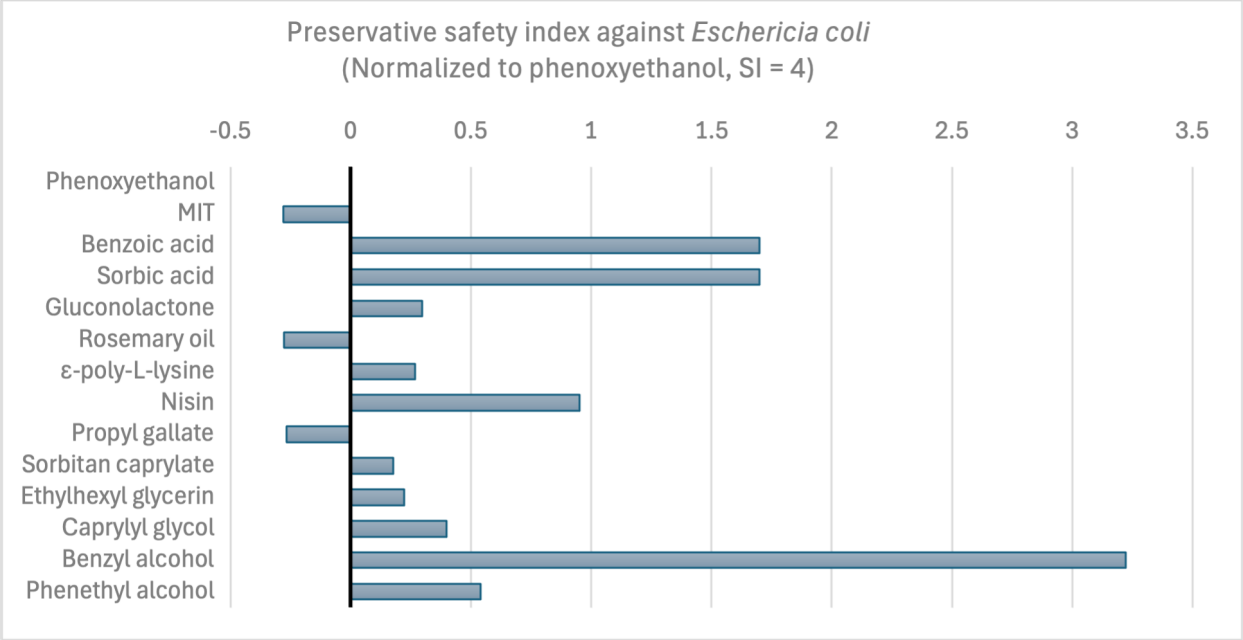


Figure 10.4. Preservative safety index against *Pseudomonas aeruginosa* for all chemicals.

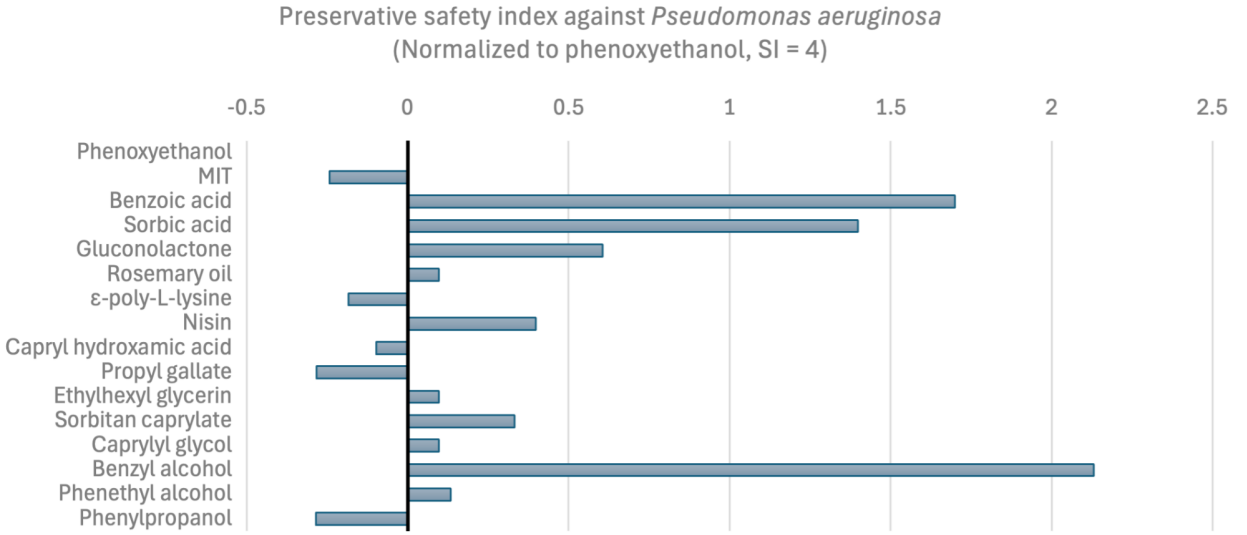
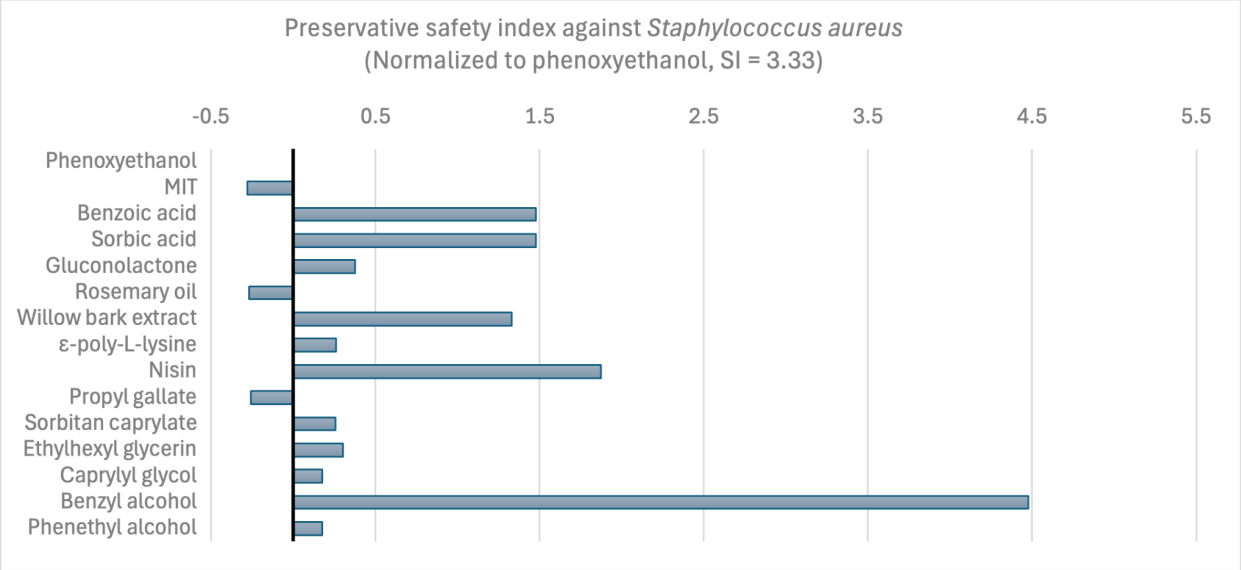


Figure 10.5. Preservative safety index against *Staphylococcus aureus* for all chemicals.



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11. Hazard Assessment: Human & Environmental Health

A comparative hazard assessment was completed using the procedure discussed in the approach section of this report. Defining a similar hazard profile as a roughly equal number of high and medium hazards, a few alternatives can be considered to have a similar or better hazard profile than phenoxyethanol. These include sodium benzoate, potassium sorbate, gluconolactone, sorbitan caprylate, ε-poly-L-lysine, sorbitan caprylate, and caprylyl glycol. Main differences between these alternatives arise in human health, and gluconolactone and peptides strike out as the only alternatives in this subset that also improves on eye irritation (albeit with low confidence)—a key issue with phenoxyethanol.

Table 11.1. Human, Environmental, and Physical Hazards for all chemicals discussed in this report

	Human Health Group I					Human Health Group II									Environmental Health		Environmental Fate		Physical Hazards	
	C	M	R	D	E	AT	STS	STR	NS	NP	SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
Phenoxyethanol[1]	**L**	**L**	L	**M**[2]	*L*	**M**	M	**L**	**M**	*L*	**L**	*L*[3]	**L**	**H**	**L**	*L*	**vL**	**vL**	*L*	**L**
MIT [4]	*L*[5]	**L**[6]	**L**	**L**[7]	DG	**vH**	M	DG	**L**	M	**H**[8]	*L*[9]	**vH**[10]	**vH**	**vH**	**vH**	*L*	vL	*L*	*L*
Sodium benzoate	*L*[2,11]	**L**[12]	DG	*L*[13]	DG	*L*[14]	**L**[15]	**L**[16]	*L*[17]	*L*[17]	**H**[18]	*L*[14]	*L*[15]	**H**[14]	*L*[19]	DG	**L**[19]	**L**[19]	DG	**L**[20]
Potassium sorbate	**L**[11,21]	*M*[22]	**L**[23]	**L**[23]	DG	**L**[24]	**L**[25]	**L**[25]	*L*[26]	*L*[26]	**L**[21]	**L**[21]	**L**[21]	**H**[27]	**M**[28]	**M**[28]	**vL**[28]	**vL**[27]	*L*[26]	**L**[26]
Gluconolactone[1]	*L*	*L*	*L*	**L**	DG	**L**	**L**	**L**	DG	DG	*L*	DG	*L*	*L*	**L**	*L*	**vL**	*vL*	*L*	**L**
Rosemary Essential Oil	DG	*M*[29,30]	*H*[31]	*H*[31]	DG	**L**[31,32]	DG	**M**[33]	DG	DG	M[34]	DG	*L*[35]	DG	DG	DG	**L**[36]	DG	DG	DG
Willow Bark Extract	**L**[42,43]	**L**[20,43]	DG	DG	DG	**L**[20,43]	DG	DG	DG	**L**[44]	*L*[43]	DG	**L**[43,45]	*L*[43]	L[43]	DG	DG	DG	*L*[43]	*L*[43]
ε-poly-L-lysine	*L*[37]	*L*[38]	*L*[39]	*L*[40]	DG	**L**[38]	*L*[38]	*L*[38]	*L*[39]	DG	*L*[40]	*L*[40]	*L*[40]	*L*[40]	*L*[40]	*L*[40]	DG	DG	*L*[40]	*L*[40]
Nisin	*L*[41,42]	*L*[43]	*L*[43]	*L*[43]	DG	*L*[44]	*L*[44]	*L*[44]	DG	DG	*M*[45,46]	*L*[45]	*L*[45]	*L*[45]	DG	DG	DG	DG	*L*[45]	*L*[45]
Capryl hydroxamic acid[47]	DG	*L*[48,49]	DG	*L*	DG	*L*	DG	*M*	DG	*DG*	*L*[48]	DG	**L**	*H*[48]	*H*[50]	*H*	**vL**	*vL*	*L*	*L*
Sorbic hydroxamic acid	DG	DG	DG	DG	DG	*L*[52]	*M*[11]	DG	DG	DG	*H*[54]	DG	*H*[53,54]	*H*[53,54]	DG	DG	DG	DG	DG	DG
Sorbitan caprylate[55,56]	**L**	**L**	**L**	**L**	DG	**L**	**L**	DG	**L**	**L**	**L**	**L**	**L**	DG	**M**	**M**	**L**	**L**	*L*	**L**
Propyl gallate[55]	L	*L*	*L*	*L*	*H*	**M**	DG	DG	DG	DG	**H**	DG	**M**	vH	**vH**	**vH**	H	**L**	DG	DG
Ethylhexylglycerin[1]	*L*	*L*	*M*	*L*	DG	**M**	**M**	*M*	*L*[57]	*L*	M	DG	**L**	**vH**	**M**	**M**	*M*	**vL**	*L*	**L**
Caprylyl glycol[1]	*L*	**L**	*L*	**L**	*L*[58]	**L**	*L*[58]	**L**	**M**	**L**	**L**	DG	**L**	**H**	*H*	*M*	**vL**	**vL**	*L*	**L**
Benzyl alcohol	**L**[1,59]	**L**[1]	**L**[1]	*M*[1]	DG	**M**[1,60]	DG	**L**[1]	*M*[1]	*H*[1]	**H**[1]	*L*[1,61,62]	**L**[1]	**H**[1]	**L**[1]	**L**[1]	**vL**[1]	**vL**[1]	*L*[1]	**L**[1]
Phenethyl alcohol	DG	**L**[3,68]	*M*[68,69]	*M*[3,68,70]	DG	*M*[69,71]	*M*[69]	**L**[3]	*M*[72]	*M*[72]	**L**[3,71]	*L*[3,72]	**L**[71]	*M*[68,71]	*M*[3]	DG	*L*[3]	*L*[3]	DG	DG
Phenylpropanol	DG	**L**[73]	L[73]	DG	*L*[74]	*vH*[74]	DG	*H*[73]	DG	DG	M[73,75]	DG	*M*[74,75]	*vH*[74]	**M**[73]	DG	**L**[73]	**L**[73]	*L*[74]	DG

Very low hazard	Low hazard	Moderate hazard	High hazard	Very high hazard	Data gap	**High confidence**	Moderate	*Low confidence*

Table 11.2. Endpoint codes for all hazard tables in report, including Table 11.1

Carcinogenicity	C
Mutagenicity & Genotoxicity	M
Reproductive Toxicity	R
Developmental Toxicity	D
Endocrine Activity	E
Acute Mammalian Toxicity	AT
Systemic Toxicity (Single)	STS
Systemic Toxicity (Repeat)	STR
Neurotoxicity (single)	NS
Neurotoxicity (repeat)	NP
Skin Sensitization	SnS
Respiratory Sensitization	SnR
Skin Irritation	IrS
Eye Irritation	IrE
Acute Aquatic Toxicity	AA
Chronic Aquatic Toxicity	CA
Persistence	P
Bioaccumulation	B
Reactivity	Rx
Flammability	F

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12. Alternative Strategies

Alternative Strategy 1: Solid Formulations (Powder and Tablets)

Inspiration

The idea of utilizing solid detergents arises from the necessity to eliminate preservatives altogether, which could reduce addressing their associated health and environmental concerns. Liquid laundry detergent formulations contain 60-80% water, are inherently prone to microbial contamination, and demand the use of preservatives to maintain safety and efficacy over long shelf life.[1] Solid detergents, such as powders and tablets, circumvent this issue entirely because without water, microbial growth is less likely. This innovative shift reflects a broader trend toward sustainable and preservative-free solutions, resonating with public health objectives and consumer preferences for cleaner, safer products (Figure 12.1).

Figure 12.1 Right: Laundry detergent in powder formulation. Source: Adobe stock images. Left: Laundry detergent in tablet formulation. Source: ROSERAY Gentle & Eco-Friendly Laundry Detergent Tablets.

Overview

Solid detergents, available as powders or tablets, are waterless formulations designed to meet cleaning and hygiene needs without requiring preservatives.[2] The absence of free water in solid detergents inherently inhibits microbial growth. Solid detergents remain stable and uncontaminated throughout their shelf life, even under varying storage conditions.[3,4] Retailers claim that laundry detergent powders and tablets do not expire unless exposed to moisture.[4] Concentrated formulations ensure high performance with small dosages, reducing product waste. Tablets dissolve quickly in water, providing convenience and consistency in dosage to guide consumers to use the correct amount of product. By eliminating the need for a preservative, this formula also reduces the risks of skin irritation, allergic reactions, and systemic toxicity associated with chemical preservatives. Solid detergents reduce exposure to preservatives such as MIT or Phenoxyethanol, aligning with consumer demand for "clean label" products. Many solid detergents can be formulated without MIT or Phenoxyethanol yet maintain efficacy. For example, Blueland's laundry detergent tablet ingredients: Sodium Carbonate, Citric Acid, Microcrystalline Cellulose, Subtilisin, Lauryl/Myristyl Glucoside, Sorbitan Caprylate/Sodium Zinc Polyitaconate, Amylase, Mannanase, Sodium Citrate, Cellulase, Hydrated Silica. Rosey's laundry detergent powder ingredients are Sodium Carbonate, Sodium Sulfate, Sodium Chloride, Sodium Carbonate Peroxide, Sodium Citrate, and Enzyme. Minimal packaging and the absence of bulky liquid containers reduce waste generation. The absence of Harmful Preservatives: MIT and

Phenoxyethanol are avoided, relying instead on the inherent stability of solid formulations and mild stabilizers such as Sorbitan Caprylate/Sodium Zinc Polyitaconate.

Remaining Questions

How readily will consumers transition from liquid products to solid formulas?

Can solid detergents achieve the same level of performance as liquid formulations in all use cases, such as personal care or industrial cleaning and varying *temperature levels?*

Alternative Strategy 2: Machine Learning for the Discovery of Novel Preservative-Booster Combinations

Inspiration

Machine learning has seen a surge of use in several industries, ranging from healthcare to agriculture. It offers a platform for learning from complex data and drawing connections that are often unapparent to humans.[5] Specifically, machine learning has been recently heavily incorporated into chemical research and has served as a useful tool to make correlations between fundamental molecular properties and chemical outcomes.[6–8] In the context of the preservative industry, machine learning has high potential to discover novel combinations that have higher potency and an improved safety profile.

Overview

When evaluating preservatives, potency and health hazards are both considered. For an extremely potent preservative with a higher hazard profile, a smaller concentration can be used to achieve desired outcomes while minimizing risk. Likewise, for a moderately potent preservative with a low hazard profile, a large concentration can be used to achieve the desired outcome with low risk. However, when the concentration required for the desired antimicrobial effect is close to or exceeds the maximum approved concentration, then alternative strategies are required. A common strategy is to combine more than one preservative, or to use a preservative booster–which is an ingredient that improves the effect of a primary preservative in a formulation.[9–11] Sometimes these combinations lead to a higher efficacy than the sum of their parts, a phenomenon known as synergy.[12] This is highly desirable, as it leads to an overall lowering of total preservative concentration, improving safety profiles and lowering costs.

Designing these systems, however, is a complicated task. There are no rational design principles for which preservatives to use with which boosters or other preservatives. Moreover, unexpected health and environmental hazard effects resulting from synergy have not been quantified or studied. Machine learning emerges as an attractive platform for investigating these questions. Preservatives and boosters are chemicals that can be represented using molecular and chemical descriptors, including structural information, geometry, free energies, pKa, etc,[13,14] which can serve as inputs for machine learning models trained to predict MIC values. These predictions can be experimentally validated by measuring MIC values of the novel preservative-booster blends,

potentially in a high-throughput manner.[15] These experimental results can then be fed back into the model for an iterative optimization cycle. An example workflow can be seen below in Figure 12.2.

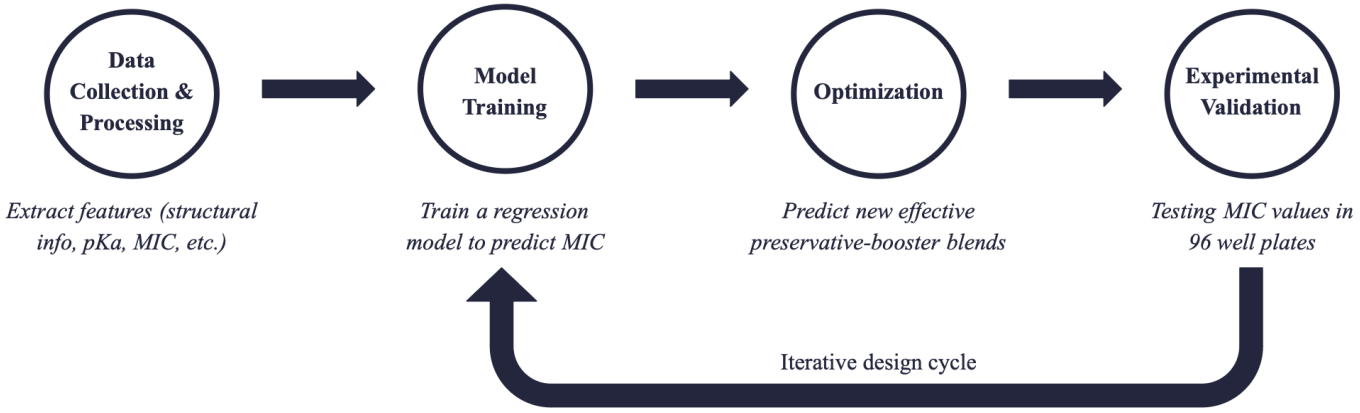

Figure 12.2. Example ML workflow for designing new effective preservative-booster blends.

Remaining Questions

If ML models are successful as predicting new preservative-booster blends with improved MIC values, can this approach be utilized to assess unexpected toxicity arising from these blends? Furthermore, can this rationale be applied for predicting formulation compatibility?

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13. Recommendations and Conclusion

We identified 5 evaluation criteria that determine the feasibility of adopting new preservatives for soaps and detergents. We assigned each proposed alternative a score of 1, 2, or 3 for each criterion according to the guidelines described in Table 13.1. Scores for the technical performance were based on the performance table in section 10 and hazards were based on the hazard table in section 11.

Table 13.1. Evaluation criteria for preservatives.

Performance Criteria	**Score**			
	3	**2**	**1**	**Data Gap (DG)**
Health Hazards	Low hazard level for most non-DG endpoints AND no endpoints with high hazard level	Medium hazard level for most non-DG endpoints OR roughly equal numbers of high and low hazard levels	High hazard level for most non-DG endpoints AND more medium than low hazard levels for remaining endpoints	More than half of endpoints are data gaps
Environmental Hazards	Low hazard level for most non-DG endpoints AND no endpoints with high hazard level	Medium hazard level for most non-DG endpoints OR roughly equal numbers of high and low hazard levels	High hazard level for most non-DG endpoints AND more medium than low hazard levels for remaining endpoints	More than half of endpoints are data gaps
Antifungal Efficacy (*Aspergillus spp.*)	≤ 100	> 100	No effect	Data gap
Antibacterial Efficacy (*P. aeruginosa*)	≤ 100	> 100	No effect	Data gap
TSCA Listed	TSCA Listed	-	Not TSCA Listed	-

Table 13.2. Comparison of preservatives using evaluation criteria from Table 13.1.

Chemical	TSCA Listed	Human Health Hazards	Environmental Hazards	Antibacterial efficacy (*P. aeruginosa*)	Antifungal efficacy (*Aspergillus spp.*)
Phenoxyethanol	3	2	3	2	2
MIT	3	1	1	3	3
Sodium benzoate	3	2	3	3	3
Potassium Sorbate	3	3	3	3	3
Gluconolactone	3	3	3	2	2
Rosemary Essential Oil	3	2	DG	2	2
Willow Bark Extract	1	3	3	DG	DG
ε-poly-L-lysine	1	3	3	3	2
Nisin	1	3	DG	3	2
Capryl hydroxamic acid	3	3	1	2	3
Sorbic hydroxamic acid	1	1	1	DG	2
Ethylhexylglycerin	1	2	2	2	2
Caprylyl Glycol	3	3	2	2	2
Sorbitan Caprylate	3	3	3	2	2
Propyl gallate	3	2	3	2	2
Benzyl Alcohol	3	2	3	3	3
Phenethyl Alcohol	3	2	2	2	2
Phenylpropanol	3	2	3	2	3

Looking at Table 13.2, only potassium sorbate received a score of 3 across all the evaluation criteria. Some of the alternatives received a score of 3 for all but one of the evaluation criteria including sodium benzoate and benzyl alcohol. Many of the other alternatives have a similar set of scores to phenoxyethanol but have different pros and cons depending on the interests of the manufacturers (Table 13.3).

Table 13.3. Proposed Strategies with Pros and Cons.

Strategy	Pros	Cons
Carboxylic Acids	- Proven in food uses - Affordable	- Need low pH - Eye irritation
Rosemary Essential Oil and Willow Bark Extract	- Naturally derived	- Willow bark is only antibacterial - pH compatibility and dosage are questionable
Peptides	- Low toxicity - Used in food preservation	- Expensive to produce - Formulation compatibility questions
Hydroxamic Acids	- Higher compatible pH range	- Ecotoxicity hazards - Understudied hazards
Esters	- Low hazards (sorbitan caprylate)	- Moderate efficacy
Polyols	- Can be used as a booster - Multifunctional (emollient properties)	- Aquatic toxicity and eye irritation - Efficacy when used alone
Phenyl Alkyl Alcohols	- Benzyl alcohol is efficacious at lower concentration	- Floral scent as a concern or use as a fragrance

Table 13.3 summarizes all the proposed alternative strategies, considering factors like efficacy, toxicity, and pH compatibility. While seven options show promise, significant challenges and uncertainties remain, such as long-term efficacy, formulation issues, economic viability, comprehensive toxicity testing, and regulatory approvals. Of these, four strategies stand out as the most viable: All of the carboxylic acids proven to be most affordable but require low pH for formulation. Peptides, such as ε-poly-L-lysine have low toxicity but are expensive. Esters, such as sorbitan caprylate have low hazards but only moderate antimicrobial efficacy. Phenyl alkyl alcohols, particularly benzyl alcohol is an effective antimicrobial agent but limited by floral

fragrance. The preliminary analysis of these alternatives requires further exploration, particularly on formulation compatibility, human and environmental hazard assessment, and partner-specific viability such as sourcing and consumer perception.

14. Appendices

Appendix A. About the Authors

Fadi Alsarhan is a PhD student in the College of Chemistry studying organic chemistry in the Toste lab. He is exploring the use of synthetic methodology for bioconjugation and chemical biology.

Carla Benato Milsted is an MS student in the College of Electrical Engineering and Computer Science. Her work aims to advance scalable and environmentally friendly solar cell technologies by exploring new methods to improve organic solar cells' efficiency, stability, and manufacturing processes.

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Appendix B. Safety Index Data

A spreadsheet containing data for safety index plots (normalized to PE and unnormalized).
See supplementary spreadsheet preservative_safety_index_data.xlsx