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Design and Testing of Safer, More Effective Preservatives for Consumer Products

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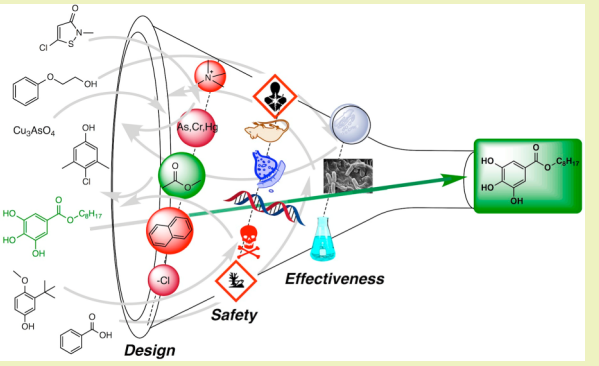
Supporting Information

ABSTRACT: Preservatives deter microbial growth, providing crucial functions of safety and durability in composite materials, formulated products, and food packaging. Concern for human health and the environmental impact of some preservatives has led to regulatory restrictions and public pressure to remove individual classes of compounds, such as parabens and chromated copper arsenate, from consumer products. Bans do not address the need for safe, effective alternative preservatives, which are critical for both product performance (including lifespan and therefore life cycle metrics) and consumer safety. In this work, we studied both the safety and efficacy of a series of phenolic preservatives and compared them to common preservatives found in personal care products and building materials. We quantified antimicrobial activity against *Aspergillus brasiliensis* (mold) and *Pseudomonas aeruginosa* (Gram negative bacteria), and we conducted a hazard assessment, complemented by computational modeling, to evaluate the human and environmental health impacts of these chemicals. We found that octyl gallate demonstrates better antimicrobial activity and comparable or lower hazards, compared to current-use preservatives. Therefore, octyl gallate may serve as a viable small-molecule preservative, particularly in conjunction with low concentrations of other preservatives that act through complementary mechanisms.



KEYWORDS: *Preservative, Antimicrobial, Safer alternative, Octyl gallate, Consumer products, Hazard assessment, Computational toxicology*

INTRODUCTION

Composite materials, formulated products, and prepared foods and their packaging all require preservatives to prevent microbial degradation. Microbial communities persist in almost any environment that offers a carbon source and water. Such environments exist nearly everywhere, from bottles of shampoo to laminate flooring. Preservatives enhance product value by prolonging the shelf life of consumables and decrease life-cycle impacts in the built environment by increasing the longevity of installed components. As consumer demand increases for bio-based and naturally derived materials,[1−4] technologies that provide safe, effective preservation against microbial attack are essential to avoid compromising shelf life, durability, or performance.[5]

There has been little work on systematically identifying classes of antimicrobial compounds that are both safer than existing options and effective microbiostats or microbiocides.[6] A patchwork of identified hazards leading to restrictions or

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marketing/labeling to improve consumer awareness has reduced the use of certain hazardous chemicals in products[7,8]—chemicals such as parabens, isothiazolinones, and metals such as chromium and arsenic. There is no comprehensive approach for proactively identifying and introducing safer alternative preservatives using meaningful sustainability metrics.[9] As health and safety information improves, there is increasing consumer and regulatory demand for safer alternatives,[6] coupled with demand for a comprehensive approach to demonstrate that these alternatives are both safe and effective.

An additional motivation for designing safe and effective antimicrobials is the evolution of resistant strains. This issue is most widely recognized in the context of concern over antibacterial compounds such as triclosan (which led to a recent FDA ban of 19 chemicals in topical antiseptics for consumers)[8] and in the emergence of resistant "superbugs" in healthcare settings.[10−12] Fungal resistance is also a growing problem,[13−15] and resistant strains of bacterial and fungal contaminants pose a challenge to both product formulators and manufacturers.[16−20] Understanding the mechanism of action as part of preservative design is one approach to overcoming microbial resistance to conventional antimicrobials.[21−23] In addition, having a broad range of potential preservatives from which to choose a synergistic mixture can help product formulators avoid inducing antimicrobial resistance.[24,25]

This paper evaluates three classes of phenolic ester/amide compounds and, by screening for antimicrobial effectiveness and human or environmental hazards, compares them to commonly used conventional preservatives. By considering chemical safety as a key performance criterion, our approach facilitates the direct evaluation of the tradeoffs inherent in selecting preservatives.[26,27] Furthermore, it provides a model for how such a multifaceted screening could be conducted for other chemistries used in consumer products, contributing to a small but growing body of literature in this area.[5,9,28−33]

There are several mechanisms by which chemical preservatives can act against microbes, which typically consist of Gram-positive bacteria, Gram-negative bacteria, or fungi (e.g., molds and yeasts). These mechanisms include binding to DNA or other anionic biomolecules, either covalently (through alkylation, e.g. by epoxides or formaldehydes) or noncovalently, interfering with transcription or damaging the DNA; protein denaturation or coagulation through changes in polarity or hydrogen bonding of the local environment (e.g., by alcohols); and disruption of redox homeostasis (e.g., by metals such as silver, or derivatized phenol compounds).[34−36] Disrupting redox homeostasis produces many outcomes, including overstimulation of oxygen uptake, disrupting ATP synthesis by interfering with electron transport chains, and uncoupling oxidative phosphorylation or active transport of protons from other processes.[34,37,38] The fine balance of redox homeostasis in cells can be disrupted by introducing or modulating the metabolism of free radicals.[39] For example, phenol compounds are potent redox cyclers in cells, which can destabilize cellular redox homeostasis and/or antioxidant systems, inhibiting the growth of microbial pathogens.[35,36,40] In particular, inhibition of glutathione reductase or superoxide dismutase enzymes or defense pathways such as the mitogen-activated protein kinase (MAPK) pathway may effectively prevent fungal growth by redox-active compounds.[41]

The inherent challenge of designing or selecting safe and effective antimicrobials for consumer products is that, by virtue of their function, antimicrobial compounds or materials must be bioactive and, therefore, often exhibit toxicity to non-microbial organisms. Many common preservatives for food packaging, personal care products, and building materials have known hazards: butylated hydroxyanisole (BHA) is a probable carcinogen;[42] parabens are known skin sensitizers[43] and have potential endocrine activity; and chromated copper arsenate is highly persistent and has a range of serious human and environmental toxicological effects.[44]

In this paper, we propose a series of potential antimicrobial compounds: phenolic acids, esters, and amides that we postulate should act through the disruption of redox homeostasis in microbial metabolism and cell components, including the cell membrane.[45,46] Our hypothesis is that small structural modifications may have differential impacts on both efficacy and human health hazards. Exploiting these differences between human and microbial biochemical processes or cell structures could improve antimicrobial potency without adverse human health outcomes. For example, selective toxicity has been achieved in fungal pathogens (ergosterol-based membrane), but not in humans (cholesterol-based membrane) by certain redox-active drugs.[47,48] We postulate that the redox activity of phenolic compounds may lead to similar differentiation of activity/toxicity. We test two classes of phenolic acid derivatives: the esters and amides of salicylic acid (2-hydroxybenzoic acid), and the esters and amides of gallic acid (3,4,5-trihydroxybenzoic acid). [We use the esters and amides of benzoic acid itself as a nonphenolic control (see Figure 1 for chemical structures).] We test a representative range of chain lengths from C_0 to C_{16} for these classes of compounds. Gallate esters have been shown to exhibit antimicrobial activity; in several cases, propyl gallate may serve as an effective alternative to salicylhydroxamic acid, which is a likely developmental toxicant.[49] Salicylhydroxamic acid works by specifically blocking the activity of alternative oxidase (AOX) in pecan scab[50] and in ethylene-treated tubers.[51]

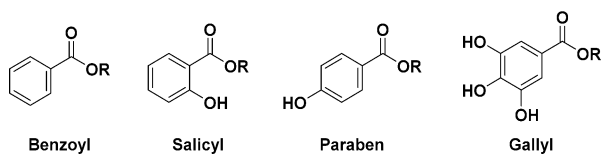

Figure 1. General structures of benzoates, salicylates (2-hydroxybenzoates), parabens (4-hydroxybenzoates), and gallates (3,4,5-trihydroxybenzoates).

We tested all of these compounds for activity against *Aspergillus brasiliensis* (mold) and *Pseudomonas aeruginosa* (Gram negative bacteria)—representative microorganisms that the health and personal care product industries use for evaluating preservative efficacy[52,53]—over a range of alkyl chain lengths to observe variability in antimicrobial activity, as a function of chain length. Of note, *A. brasiliensis* has recently been found as a causative agent of keratitis,[54] while *P. aeruginosa* can cause disease in humans,[55] thus emphasizing the importance and relevance of testing these microbes. Both of these test organisms, and related species, are known to exhibit exceptional resilience against typical antimicrobial agents.[25,56,57]

Testing a range of ester chain lengths provides useful information about the effectiveness of compounds that, due to different physical properties (e.g., water/lipid partitioning), will be compatible with different formulations and products.[58] We

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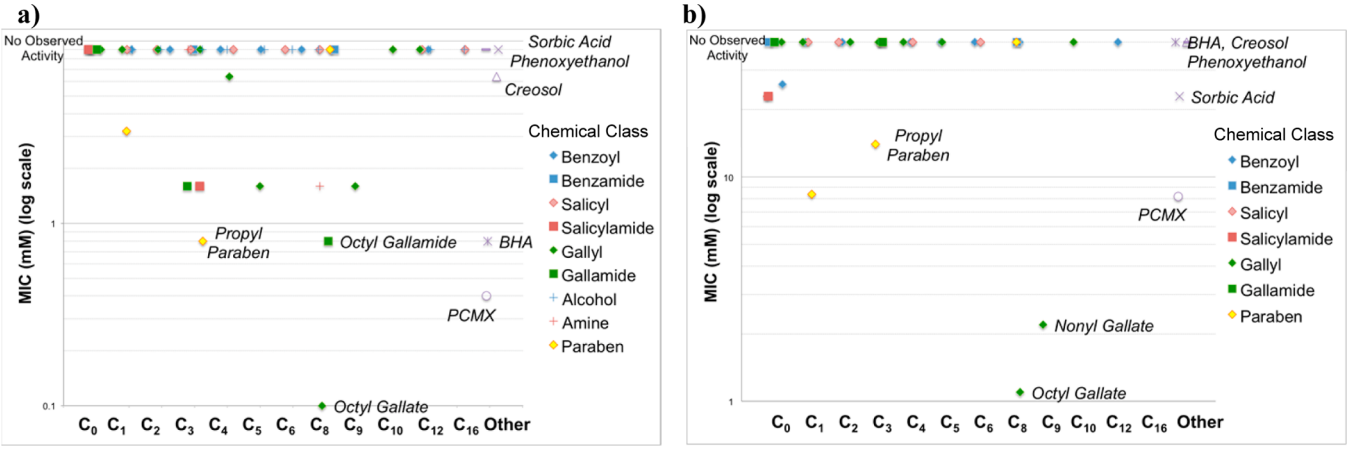
Scheme 1. (a) Antifungal Activity of Compounds Tested in *Aspergillus brasiliensis* ATCC16404;[a] (b) Antibacterial Activity of Compounds Tested in *Pseudomonas aeruginosa* ATCC9027[b,c]



[a]MIC (mM) = minimum inhibitory concentration, where no fungal growth was visible in RPMI liquid culture measured up to 6.4 mM, with exceptions due to solubility limitations noted in Table S1 in the SI. [b]MIC (mM), where no bacterial growth was detected by Abs600 measurement in Mueller−Hinton liquid culture. [c]In both panels (a0 and (b), phenolic esters and amides, alcohols, and amines are differentiated according to alkyl chain length (C_0−C_{16}), while other classes of preservatives are clustered on the right and are labeled.

tested the corresponding benzoic acids and alcohols that comprise the esters, as well as representative corresponding benzamides, to provide insight into whether hydrolyzed subcomponents, or differences in electronegativity (and, therefore, radical stabilization) could be responsible for antimicrobial activity. Finally, we tested representative preservatives that are currently used in food packaging, personal care products, and building materials, and are postulated to operate by a similar mechanism (disrupting redox homeostasis in microbial cells).[38] One of the classes of "control" molecules tested is parabens (esters of *para*-hydroxybenzoic acid); methyl and propyl parabens are widely used preservatives with structures similar to our proposed alternative compounds, but they act as dermal sensitizers.[59]

To complement this evaluation of antimicrobial effectiveness, we conducted a hazard assessment of a representative subset of our proposed preservatives, and compared them to common preservatives, as discussed above. Our evaluation is based on the same principles as a GreenScreen assessment,[60] drawing information from a combination of authoritative lists and compiled primary literature on hazard end points. In the absence of available data, we used computational tools to make structure-related predictions.

Overall, this study demonstrates a method for systematically comparing both antimicrobial effectiveness and hazards to human health and the environment, which are two crucial parameters in sustainable material selection. It provides information that can help formulators make informed decisions about proposed alternative preservatives. It also demonstrates a more general strategy for evaluating both the safety and efficacy of other ingredients used in materials and consumer products.

MATERIALS AND METHODS

Full experimental details for chemical synthesis, microbial assays, hazard analysis, and computational toxicology can be found in the Supporting Information (SI).

Alkyl esters and amides of varying chain lengths of benzoic acid, salicylic acid, and gallic acid, along with the acids, alcohols, and amines that are their functional constituents, were either synthesized or procured from commercial sources. When possible, solventless reactions and purifications using safer solvents were favored (see the SI for details).[61−63] To the extent possible, C_0−C_6, C_8−C_{10}, C_{12}, and C_{16} benzoate esters were prepared or procured, along with C_0, C_3, and C_8 amides (those omitted were not readily available and synthetically impractical to prepare, and as such of minimal relevance to possible widespread application). To complement these, three preservatives used in personal care products (phenoxyethanol, methyl paraben, and propyl paraben), octyl paraben, two preservatives used in food and food packaging (sorbic acid and BHA), and two preservatives used in wood and composite material products (chloroxylenol and creosol) were obtained.

Esters of salicylic acid and gallic acid were chosen for this study, because they are phenolic compounds, capable of forming a relatively stable phenol radical and, therefore, are capable of acting through disruption of the redox homeostasis.[64] They are broadly available and therefore realistically applicable to industrial product formulation. Salicylates were specifically chosen as a complement to widely used 4-hydroxybenzoates (parabens) to study whether a structural analogue could be safer and an equally or more effective preservative. Esters of benzoic acid were included as a control, to understand the antimicrobial efficacy of the benzoate group in the absence of a phenol group.

Hazard analysis was conducted by systematically reviewing authoritative lists, toxicology literature, and online databases, particularly Pharos (Healthy Building Network)[65] and the Hazardous Substances Data Bank (HSDB, National Library of Medicine)[66,67] for existing information regarding human health and environmental hazard end points for representative compounds. End points were grouped in a similar manner to the end points in GreenScreen,[60] in keeping with listings by authoritative bodies. In addition, physical properties of note (including log *P* values) and listings on restricted lists or safer alternative designations are included for reference. In the absence of comprehensive hazard information, computational toxicology methods were used to fill in data gaps with structure-based predictions. Data were collected for a subset of compounds using PBT Profiler,[68] the ADMET Predictor,[69] Lhasa Derek,[70−72] the Endocrine Disruptor Screening Program for the 21st Century,[73] OECD QSAR Toolbox,[74] and Toxtree[75] software suites. See the SI for additional details.

RESULTS AND DISCUSSION

Antifungal Activity. Scheme 1a displays minimum inhibitory concentrations (MICs) for all of the potential

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antimicrobial compounds tested against *A. brasiliensis* ATCC16404. Full MIC and minimum fungicidal concentrations (MFC) data are shown in Table S1 in the SI.

At the concentrations tested, none of the esters or amides of benzoic acid showed any antifungal activity. This is not surprising, because these compounds contain no phenol groups to stabilize free radicals that might disrupt redox homeostasis.[76] In addition, none of the esters of salicylic acid exhibited antifungal activity; this finding indicates that the presence of phenol is not a guarantee of significant disruption of redox homeostasis, which is consistent with previous reports.[77] It is possible that this reduced activity can be attributed to steric inaccessibility of the hydroxyl group *ortho-* to the ester, reducing the ability to form a phenol radical and influence the oxidative stress response. Esters of gallic acid with alkyl chain lengths of four or more carbons inhibited growth of *A. brasiliensis*, with the maximum efficacy observed for octyl gallate (MIC = 0.1 mM); this MIC was the greatest antifungal efficacy observed for any preservative tested in this study, including compounds currently in commercial use. The correlation of antifungal activity with chain length for short-chain esters is consistent with previous studies of 4-hydroxybenzoic acid against *A. brasiliensis*.[78] Pentyl gallate and octyl gallate also exhibited fungicidal activity (MFC = 6.4 and 0.4 mM, respectively; see Figure S1 in the SI for a representative display/bioassay, and see the SI for calculation).

While none of the alcohols or benzoic acids tested in this study showed fungistatic or fungicidal activity up to the concentrations tested, the phenolic alkyl amides (*N*-propyl salicylamide, *N*-propyl gallamide, and *N*-octyl gallamide) demonstrated inhibition of growth at 1.6, 1.6, and 0.8 mM, respectively. None of these compounds exhibited fungicidal activity. (See the SI for calculation.)

The better performance of *N*-propyl amides over the corresponding esters can be explained by the following arguments:

(1) slow rates of amide hydrolysis, which could result in greater bioaccumulation of amides relative to esters (the lack of activity of *N*-propyl benzamide suggests that the inhibitory activity of these compounds is not simply due to the presence of the amide group),[79] and

(2) enhanced resonance stabilization of a free radical by an amide relative to an ester,[58] which is a property that is attributable to the inherently greater stability of a nitrogen-based radical over an oxygen-based radical.[80]

Similar arguments explain the greater antioxidant capacities of amides, compared to their ester-containing analogues.[58] None of these explanations accounts for the greater antifungal activity of octyl gallate relative to *N*-octyl gallamide. However, gallates have been shown to inhibit alternative oxidase (AOX) activity in the fungal mitochondrial respiratory system, where they possess higher binding affinities than the corresponding gallamides. This mechanism of action may predominate in the interaction of octyl gallates.[81−86]

The antifungal activity of octyl gallate (MIC 0.1 mM, MFC 0.4 mM) compares favorably to all of the food preservatives tested: sorbic acid, gallic acid, and benzoic acid showed no activity under the conditions tested, while BHA (butylated hydroxyanisole), which is a phenol and therefore presumably also acting through the disruption of redox homeostasis,[64] had an MIC value of 0.8 mM (no fungicidal activity by calculation) at the concentrations tested (see Figure 2 and Table S1 in the SI).

Similarly, octyl gallate and several of the other gallates tested have comparable or better performance than the preservatives conventionally used in personal care products. 2-Phenoxyethanol shows no activity at the concentrations tested, while methyl and propyl 4-hydroxybenzoate, the two most widely used parabens, have MIC values of 3.2 and 0.8 mM, respectively (no fungicidal activity by calculation) (see Figure 2 and Table S1). Interestingly, octyl paraben shows no fungistatic or fungicidal activity at the concentrations tested; this is in contrast to octyl gallate and other medium-chain gallates, which show significant activity. While octyl gallate has been approved for some time as an antioxidant food additive in the United States,[87] and the broader antimicrobial activity of this compound has been documented,[88−90] the superior antimicrobial potency of gallates, compared to other phenolic esters, is a new finding.

Copper arsenate, which is a widely used wood preservative, was not tested in this study, because of the known high acute human health hazard. However, PCMX (4-chloro-3,5-xylenol) and creosol (2-methoxy-4-hydroxybenzoate) were tested and found to have MIC values of 0.4 and 6.4 mM, respectively; PCMX shows a MFC value of 1.6 mM. Both were less effective than octyl gallate in these experiments.

Antibacterial Activity. Scheme 1b shows MICs for all of the potential antimicrobial compounds tested against *P. aeruginosa*. Full MIC data are shown in Table S2 in the SI.

Using *P. aeruginosa* as an example of an industrially challenging bacterium,[52] we first determined differences in MICs among the three structural classes. Among benzyl, salicyl, and gallyl esters, the gallyl esters exhibited the highest antibacterial potency. This observation parallels the results of *A. brasiliensis* antifungal assays. These trends are also consistent with previous reports examining the antimicrobial efficacy of substituted benzaldehydes, where increasing −OH substitution generally resulted in greater potency.[91]

We next considered the influence of R-group chain length on antibacterial efficacy. Within the gallate class, antimicrobial efficacy was high for octyl and nonyl gallate, but low for all other gallates. Although imperfect solubility limited determination of any trends for the lighter gallates (see the SI), structure−activity relationships indicating increased activity at moderate chain lengths have been widely reported for fatty acids and other antimicrobial substances.[1,34,92]

It has previously been reported that carboxylic acids exhibit antimicrobial properties, since bacteria have a tendency to exhibit higher sensitivity to bulk solution acidity than molds.[93,94] The three acids exhibited modest activity. This finding can be attributed to the combined effects of substance action and broth acidification, because the addition of acids to broth caused a small but consistent shift in Mueller−Hinton broth acidity, by approximately one pH unit at a concentration of 1 wt %.

Parabens generally exhibited greater potency than isomeric salicyl esters (4-hydroxybenzoates vs 2-hydroxybenzoates). This result suggests that either differences in sterics, or increased potential for hydrogen bonding in a 2-hydroxy-substituted benzoate may play a role in antimicrobial activity.

Octyl and nonyl gallate performed favorably, in comparison to most antimicrobials used commercially. While the parabens also function as better antimicrobials than other species tested, microbial resistance to parabens has been documented, with active efflux of parabens out of the cell as the proposed

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Table 1. Summary of Hazard Information for Proposed Alternative Preservatives, Compared to Preservatives Currently Used in Personal Care Products, Building Materials, and Food Packaging[a]

Common/ Trade Name	CAS Number	Group I Endpoints	Group II Endpoints	Group II* Endpoints	PBT Ecotox
Proposed Alternative Preservatives					
Gallic acid	149-91-7	Low	Low	Moderate	Low
Propyl Gallate (E310)	121-79-9	High#	High	High	Moderate
Octyl Gallate (E311)	1034-01-1	*Moderate*#	High	High	*Very High*#
Lauryl Gallate (E312)	1166-52-5	*Moderate*#	Moderate	High	Moderate
Personal Care Products					
Phenoxyethanol	122-99-6	High	Moderate	Moderate	Moderate
[Parabens - Methyl, propyl, butyl]		High	Moderate#	Moderate	Moderate
Wood/Building Products					
Copper Arsenate [Cu3(AsO4)2]	10103-61-4 /16102-92-4	Very High	High	Moderate	Urgent
Chloroxylenol (PCMX)	1321-23-9/ 88-04-0	High	High	High	Very High
Creosol (2-methoxy-4-methylphenol)	93-51-6	*Low*#	Moderate	Moderate	Moderate
Food and Food Packaging					
Sorbic acid E200	110-44-1	Very High#	Low	Moderate	Moderate
BHA (E320)	25013-16-5	Very High	Moderate	High	High
Benzoic acid	65-85-0	Very High	Moderate	High	High

[a]In this table, data are taken from authoritative lists and literature review. Our full hazard assessment, including information sources, is available in the SI (Table S3). The level of hazard in each broad class is determined based on the highest hazard indicated under the subcategories of that class. Level of hazard is denoted by color: (Urgent Concern to Avoid through Low Hazard: Purple, Red, Orange, Yellow, Green); the intensity of the color is a direct indicator of the certainty (the greater the intensity of the color, the greater the certainty of the measurement). Information denoted with a hashtag (#) superscript indicates a hazard designation based primarily on computational toxicology.

mechanism of antimicrobial resistance.[95] The building material preservative PCMX (4-chloro-3,5-xylenol) exhibited good potency, which was nonetheless exceeded by octyl and nonyl gallate. Similarly, preservatives for food packaging and home and personal care products such 2-phenoxyethanol, benzoic acid, gallic acid, and sorbic acid inhibited the growth of *P. aeruginosa* at comparable concentrations to many gallates with the exception of octyl gallate, which was much more potent.

Hazard Assessment. Several frameworks exist for comparing chemical hazard to human health and the environment.[96] Our approach to searching for hazard data using authoritative lists and toxicology literature closely follows that of GreenScreen,[60] which is a chemical hazard assessment method developed by the NGO Clean Production Action. We chose GreenScreen as a basis for our hazard analysis because (i) its methodology is publically available and (ii) its approach is consistent with the European Chemicals Agency (ECHA) guidance for alternatives analysis under REACH[97] and the U.S. Environmental Protection Agency's Design for Environment (DfE) chemical assessment framework.[98] It uses hazard classifications based on the Globally Harmonized System (GHS) of the United Nations.[99] This hazard-based approach, without presuming specific use cases and therefore limiting exposure estimates, considers a range of ecological and human health hazards.

Our hazard assessment compiles available information on human health and environmental hazards, grouped into four categories by type of hazard end point, consistent with groupings established by authoritative bodies.[60] Group I end points (carcinogenicity, mutagenicity, reproductive and developmental toxicity, and endocrine toxicity) are those that can have serious chronic effects, some of which may be heritable, Group II (acute) and II* (chronic/sublethal) are hazards that can potentially be moderated through exposure controls or have their impacts be reduced through medical treatment. The environmental fate and toxicity (PBT) category refers to persistence, bioaccumulation, and toxicity in various ecosystem media, with aquatic toxicity being the most commonly highlighted due to the mobility of toxicants in waterways.

We focused our hazard assessment on representative compounds from the classes we tested, considering the free acid, propyl, octyl, and dodecyl esters of the three classes of phenolic compounds, as well as all of the commercially used preservatives in the study. Table 1 summarizes the hazard information that we have gathered from the literature and authoritative lists.[67,68,100] A full version of our hazard assessment, including information on all end points and

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information sources for all classes of chemicals considered, is given in the SI (Table S3).

Incomplete hazard information for many of these chemicals decreases the certainty of their hazard designations. An absence of data should never be taken to imply an absence of hazard. However, in situations where information is available, some comparisons can be drawn between classes or structural features of chemicals, and these comparisons can be used to inform decisions about product formulation.

In cases where reliable toxicological information is not available from the literature or authoritative lists, computational toxicology models can supplement existing data with chemical hazard predictions.[101−104] Tables S4 and S5 in the SI contain complete list of the computational toxicology metrics used and their outputs. We include computational results in Table 1 only in the absence of other data. To draw relevant conclusions based on computations, we determined results for the relevant end points for several representative gallates and all non-metal-based commercial preservatives; these are discussed in the following section. Chromated copper arsenate was not evaluated with computational tools because, in general, tools for the evaluation of human health impacts of metals and metal-containing compounds are still fairly limited, and the majority of available tools focus on environmental impacts and the fates of metals.[105−107] Because toxicological data abound for chromated copper arsenate, a full hazard assessment is still possible.

Computational Toxicology. All of the compounds analyzed triggered at least one structural alert or were predicted to cause human toxicity in QSAR models during *in silico* testing. This result is not surprising, because these compounds are bioactive by design. Trade-off decisions between efficacy and hazard reduction are sometimes necessary. When programs disagreed with their predictions for toxicity, we prioritized more-specific structural alerts (i.e., from Derek). Within those results, we gave precedence to the more conservative prediction of toxicity.

Sorbic acid and phenoxyethanol were the only compounds not predicted by any method to have endocrine toxicity, while the parabens, chloroxylenol, and 3-*tert*-butyl-4-methoxyphenol were all predicted to have mild to moderate endocrine activity. Only the OECD QSAR Toolbox predicted strong estrogen receptor binding for the gallates. The Toolbox uses a small set of structural criteria (molecular size, number of carbon rings, presence of OH or NH_2 groups, etc.), which is different from the more-specific structural criteria used by Derek to predict toxicity, resulting in more conservative predictions than other platforms.[104] The EPA EDSP21 platform also predicted weak or very weak estrogen receptor binding for creosol, the gallates, the parabens, and chloroxylenol based on QSARs and available literature; the platform did not predict estrogen receptor binding for phenoxyethanol or sorbic acid, and could not assess 3-*tert*-butyl-4-methoxyphenol.

Literature evidence on the endocrine activity of gallic acid and the corresponding esters varies.[73,108−115] Recent reviews from the European Food Safety Authority found that, of the three gallates we evaluated, only propyl gallate was of potential concern as an endocrine disruptor.[111,112,116] Octyl gallate was not found to affect endocrine receptor activity in the experimental system used by Amadasi et al., but there is some evidence that it can inhibit 5α-reductase and thus influence androgen regulation.[115,117] Propyl gallate did not inhibit 5α-reductase in this system; lauryl gallate was not studied.[115] Generally, experimental data agree with the majority of *in silico* models. Both indicate that, while there is abundant evidence suggesting propyl gallate to be an endocrine disruptor, evidence for octyl gallate is weaker and requires more thorough investigation. There is no evidence that lauryl gallate acts as an endocrine disruptor.[110,118−121] However, sufficient data gaps exist that no conclusions should be drawn about the relative endocrine disrupting potential of gallates of different chain lengths.

All compounds tested were predicted to cause sensitization or irritation of dermal or respiratory tissues by at least two of the five *in silico* platforms used. Phenoxyethanol triggered only the OECD QSAR Toolbox alert (for ethylene glycol ethers) and skin irritation alerts in Toxtree. ADMET predicted that all gallates, sorbic acid, creosol, and chloroxylenol were likely skin irritants and sensitizers; the parabens, phenoxyethanol, and 3-*tert*-butyl-4-methoxyphenol were predicted to be nonsensitizers. Predictions of skin irritation/sensitization by Derek and ADMET were in agreement for creosol and the gallates, except gallic acid, which did not trigger any structural alerts in Derek. Predictions from Derek differed from those of ADMET for sorbic acid, 3-*tert*-butyl-4-methoxyphenol and the parabens, predicting that sorbic acid and the parabens were less likely to be skin sensitizers than the gallates, while chloroxylenol and 3-*tert*-butyl-4-methoxyphenol were comparable to the gallates. While there is some concern for skin sensitization with the gallates, they are comparable or slightly better than existing antimicrobials for this end point.

Overall, computational results for the gallates were comparable to several currently used preservatives that are known to cause skin sensitization, and they are predicted to have less (if any) endocrine activity, compared to the parabens and chloroxylenol.

Comparison of Benzoate Esters. In cases where data are available, the structural similarities among various phenolic esters match the hazard properties. The esters of benzoic acid, salicylic acid, and gallic acid, as well as the parabens, differ primarily in the number and position of hydroxyl groups. Where data are available, there is moderate evidence of endocrine disruption (a Group I end point) for many of these compounds.[104,110,111,120]

There is also moderate evidence of skin sensitization, skin irritation, and/or eye irritation for most benzoate esters, based on both authoritative lists and computations. These hazard end points are of particular concern in home and personal care products, but are also of concern for workers who handle building materials or food packaging.[112−114,122−124] Our computational modeling supports this evidence; further differentiation of the degree of skin sensitization expected from a related group of compounds could be obtained with modeling that is specifically optimized around skin sensitization predictions, such as CADRE-SS developed by Kostal and Voutchkova-Kostal[125] or nuclear magnetic resonance (NMR) correlations of skin permeation with spectroscopic properties.[126]

The potential health effects of phenolic esters differ with changing chain length. Bioavailability has a tendency to be lower with increased molecular weight, while increased partitioning to lipids (increased bioconcentration factor) has a tendency to accompany the presence of longer hydrophobic chains. Microbial degradation of related esters can be rapid and offset tendencies to bioaccumulate.[127] In addition, molecular weight/chain length are completely independent of some

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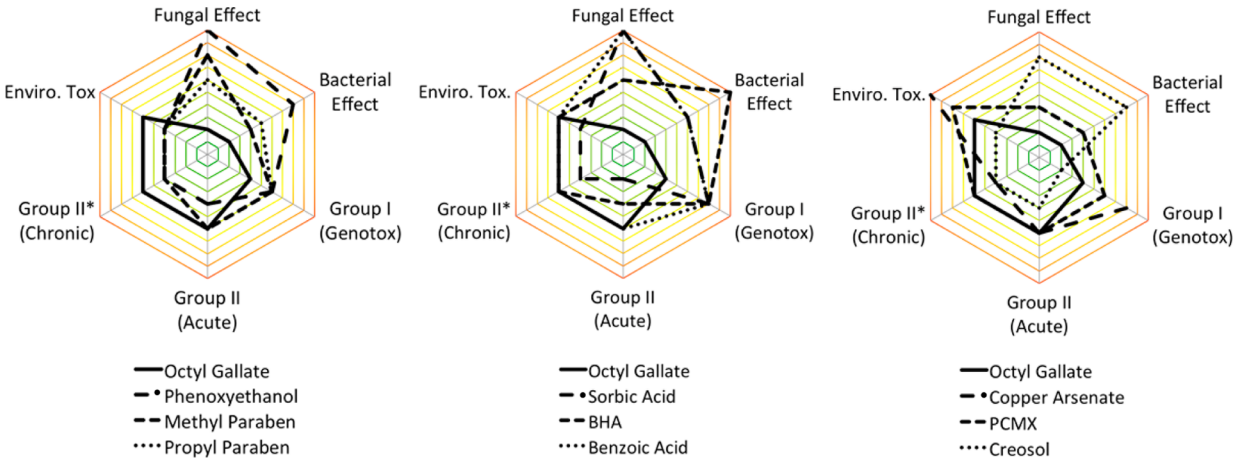

Figure 2. Spider diagrams comparing hazard and effectiveness of octyl gallate to common commercial preservatives in three applications: (a) home and personal care products, (b) food packaging, and (c) building materials. Smaller values (closer to the center of the spiderweb) are indicative of better performance on each of the six metrics, i.e., lower MIC and MFC indicate greater antimicrobial effectiveness, and lower hazard in each broad category.

modes of bioactivity; Uramaru et al. have shown that medium-length parabens demonstrate higher histamine responses, compared to short-chain parabens.[43] Uramaru et al. also find significantly lower histamine activity for octyl salicylate and octyl-3-hydroxybenzoate, compared to octyl paraben, demonstrating that substituent position can significantly change biological activity in otherwise very similar compounds. These types of distinctions underscore the importance of understanding the potential health effects of any chemical that may be introduced into commerce.

Comparison of Octyl Gallate and Current Commercial Preservatives. Octyl gallate is highly effective as both an antibacterial and antifungal compound, outperforming other proposed alternative preservatives, as well as those currently widely used in consumer products. As such, the remainder of this discussion of hazard will focus on a comparison of octyl gallate to the materials currently used in home and personal care products (parabens and phenoxyethanol), food packaging (sorbic acid, BHA, and benzoic acid), and building materials (chromated copper arsenate, PCMX, and creosol) that were evaluated. Figure 2 shows spider diagrams that visualize the relative hazard under each major category of human health/environmental end point, as well as the effectiveness of each compound against bacterial and fungal growth as established in this study. As outlined above, literature data in this section is obtained from sources within the Pharos database[65] and the Hazardous Substances Database (HSDB).[67] Detailed source information is found in Table S3 in the SI.

Home and Personal Care Products. Figure 2a shows spider diagram data for home and personal care products. To the extent that hazard data are available, the hazard traits of gallates mirror the structurally similar parabens. Both show some evidence of skin sensitization, as well as skin and eye irritation. As discussed above, computational results demonstrating possible endocrine disruption are mixed for the gallates. The balance of evidence suggests that gallates may be less hazardous on this end point, compared to parabens.

While available data indicate a lack of carcinogenicity, mutagenicity, and reproductive/developmental toxicity for parabens and for octyl gallate, computational predictions suggest potential mammalian carcinogenicity and chromosomal damage by gallates. The redox-active structures of these compounds are likely responsible for both this toxicity and their higher antimicrobial activity, postulated to occur through the disruption of redox homeostasis or of redox-sensitive cellular components such as cellular membranes. Previous studies support this hypothesis: antioxidant gene mutants of the yeast *S. cerevisae* demonstrated high susceptibility to treatment with known disruptors of redox homeostasis,[128,129] including octyl gallate.[64] By taking advantage of biochemical differences between complex eukaryotes and the microbes responsible for spoilage,[130] we can adjust molecular properties of redox-active molecules to favor toxicity in simpler organisms but not in humans. This has been achieved with the oxidative antifungal drug amphotericin B (AmB), which binds to fungal but not human cell membranes, allowing for selective toxicity to fungal cells.[47,48]

Characteristics such as potential redox activity of the compounds highlight the challenges and opportunities for making bioactive molecules that are inherently safer for humans.[111,113,124] To comprehensively assess all of these compounds for genetic toxicity, OECD guidelines recommend extensive *in vitro* and *in vivo* testing, including chromosomal tests and oral dosing in rats;[131,132] this assessment has not been completed for these compounds.

Phenoxyethanol is a widely used "safer" alternative to parabens and other conventional preservatives in home and personal care products; however, it is also a suspected human reproductive and developmental toxicant.[133] Unlike octyl gallate, there are no direct indications of mutagenicity, although an Ames test (a predictor of mutagenic activity)[134] for analogous butoxyethanol suggests possible mutagenicity.[135] Unlike the parabens, phenoxyethanol is not flagged on any authoritative list as a skin sensitizer or irritant; computational predictions are consistent with this observation. Skin sensitization/irritation is a major concern to consumers of home and personal care products, but also are a concern for workers in industrial cleaning, as well as food handling and manufacturing. Computational data do not predict that phenoxyethanol would have significant estrogenic or androgenic activity. This information suggests that phenoxyethanol is a safer choice than parabens, in terms of endocrine disruption; it is likely to be comparable to or better than octyl gallate for endocrine disruption as well.

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Food Packaging. Figure 2b shows spider diagram data for food packaging. Among the preservatives used in food packaging, sorbic acid is the only compound examined that has low acute toxicity; octyl gallate is acutely toxic but is also approved for use in food (as an antioxidant), suggesting that all of these compounds are toxic at concentrations significantly above that found in packaging. At least one study indicated that potassium sorbate (the potassium salt of sorbic acid) is genotoxic to human lymphocytes.[136] All of these compounds are potential skin sensitizers or irritants. BHA stands out as a compound that is a priority for substitution, because of its classification as a probable carcinogen by the U.S. National Institutes of Health (NIH) and International Agency for Research on Cancer (IARC). Computational predictions suggest that octyl gallate may plausibly cause chromosome damage in mammals.[137] These same predictive methods also suggest that BHA is a plausible carcinogen; more research is needed to understand the relative genotoxic hazards of octyl gallate, as opposed to BHA, although other aspects of genotoxicity (such as developmental toxicity) are unlikely for octyl gallate, based on computational toxicology. BHA and benzoic acid both appear on authoritative lists as potential endocrine disruptors; computational data support the potential for BHA to act as both an estrogen and androgen mimic.

Building Materials. Figure 2c shows spider diagram data for building materials. If it were used in pure form, creosol would potentially be the least harmful of the widely used preservatives used in building materials; where information is available, it is less hazardous than octyl gallate on nearly all end points. However, its typical use is as a component of creosote, which is recognized by IARC and the U.S. Environmental Protection Agency (EPA) as a probable carcinogen, in addition to having acute toxic effects and causing damage to mucous membranes.[67] Little information is available in the literature about the Group I health end points associated with creosol itself; computational models indicate that, unlike octyl gallate, it does not trigger alerts for potential genotoxicity. Creosol is not predicted to be an estrogen or androgen mimic, but it does trigger alerts in Derek for possible hepatotoxicity. Like most other compounds considered in this study, creosol is a skin and eye irritant.

From a human and environmental toxicity perspective, additional clear-cut cases for the need for safer alternative preservatives in building materials are PCMX and chromated copper arsenate. Similar to other currently used preservatives, PCMX is acutely toxic, a potential endocrine disrupter, and a skin sensitizer and irritant. Copper arsenate (used as chromated copper arsenate, because chromium improves the binding of the copper arsenate to wood and composite materials) is a known carcinogen (IARC Group 1), a mutagen, a reproductive toxicant, and developmental neurotoxicant, and is acutely toxic. In addition to various health concerns, both PCMX and copper arsenate are persistent in the environment: PCMX, because of the low biodegradability of the organohalogen functionality, and copper arsenate, because it is an inorganic compound and, therefore, inherently persistent. Replacing each of these preservatives with safer alternatives such as octyl gallate or phenoxyethanol has the potential for positive human and environmental health and safety implications.

CONCLUSIONS

As a potential alternative preservative for home and personal care products, composite building materials, and food packaging, octyl gallate (octyl 3,4,5-trihydroxybenzoate) shows promising antimicrobial activity against representative mold and bacteria, with greater efficacy than common commercial preservatives currently used in these applications. While not as striking, other hydroxyl-substituted benzoic acids also show some antimicrobial activity, particularly against bacteria. Based on these results, we conclude that several design parameters exert a significant effect on the antimicrobial potencies of resulting substances:

(1) alkyl chain length—this effect may be due to surfactant action, association with biomolecules, and changes in hydrophilicity or aqueous partitioning;
(2) position of phenol substitution (specifically, 2-hydroxybenzoates versus 4-hydroxybenzoates); and
(3) the number of hydroxybenzoates (singly versus triply hydroxylated benzoates).

These results are promising, because, although gallates are not completely free of potential hazards to human health and the environment, a systematic screening of authoritative lists and primary literature, supplemented by computational toxicology, suggests that octyl gallate and its structural analogues have hazard profiles that compare favorably to those of many commercial preservatives. Their potent antimicrobial and antifungal properties may make them effective at lower concentrations than current-use preservatives, reducing potential exposure. Taken together, these results indicate that it would be worthwhile to further explore the use of octyl gallate in consumer products, including health and efficacy testing on formulated products as a single ingredient and as part of a mixture of preservatives acting through complementary mechanisms. The propensities of octyl gallate and other compounds for skin sensitization, genotoxicity and endocrine activity through warrant further testing before they can be unconditionally recommended for use in consumer products. However, this evaluation is an important step toward incorporating inherently safer preservatives and other constituent chemicals in product design and formulation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.7b00374.

Details and results of chemical syntheses, microbial assays, hazard analysis, and computational toxicology (PDF)
(XLSX)
(XLSX)
(XLSX)

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Notes

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