Greener Alternatives to Phthalate Use in Hair Relaxer Formulation

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Executive Summary

Phthalates are widely used in plasticizers, solvents, and scent stabilizers across various industries, making them ubiquitous in many products. Due to their low cost and easy accessibility, phthalates have been commonly used for several decades until the health and environmental hazards associated with them were brought to public attention in the late 2000s. The lack of proper labeling and use of multiple phthalate compounds poses a significant challenge to regulating these chemicals. These compounds can cause various developmental and reproductive disturbances in wildlife. Humans can be exposed to phthalates through various routes, such as inhalation, ingestion, and skin contact with personal care products. At low exposure levels, phthalates can be metabolized by human bodies through a two-step metabolic pathway. However, the effects of phthalate release on the environment and human health are still a matter of concern, and precautionary measures should be taken to prevent further environmental contamination from phthalates.

The goal is to find a safe alternative to phthalates in hair relaxers. Phthalates stabilize fragrances in cosmetic products. To find alternatives, we researched alternatives that had reduced health hazards, scent stabilizing capabilities, reduced environmental impact, and economic feasibility. We evaluated all proposed alternatives according to metrics, constructed a hazard table, and ensured that all alternatives met or exceeded the performance and health metrics of phthalates in hair relaxers. We concluded that there is a landscape for phthalate alternatives, and that alternatives like coumarin, dipropylene glycol, and cellulose nanocrystals all have potential to transform the industry. We believe that cellulose nanocrystals have the most potential to be a safer alternative to phthalates.

Introduction

Phthalates are ubiquitous in many products we use in our everyday lives due to their important role as plasticizers, solvents, and scent stabilizers across a multitude of industries. As plasticizers, phthalates make plastics more durable, flexible, malleable, and temperature tolerant.[1] One such application is in polyvinyl chloride, or PVC, which is the world's third-most widely produced synthetic polymer of plastic and commonly had phthalates added as part of the manufacturing process. They are also common as solvents in shampoos, perfumes, creams, and other cosmetic products, serving as a chemical carrier and stabilizer for fragrances. The low volatility of phthalates contributes substantially to their ability to stabilize scents, allowing fragrance molecules to remain on surfaces for extended periods of time. In addition, the low cost and easy accessibility of phthalates contributed to the wide use of this chemical for several decades until the human health and environmental hazards were brought to public attention in the late 2000s. To date, phthalates are still in use, often synthesized from phthalic acid and exhibit a low production cost of approximately 1 USD per kilogram in API reference price.[27]

The lack of proper labeling and use of multiple phthalate compounds poses a significant challenge to regulating these chemicals. Since phthalates are commonly used in personal care products as part of the scent formulation, these chemicals are not required to be listed on product labels due to the proprietary nature of scents. Furthermore, the use of multiple synonyms for phthalates compounds makes it challenging for consumers to identify these chemicals in the ingredient list. The eight most widely used phthalate compounds are butyl benzyl phthalate (BBP), di-*n*-butyl phthalate (DBP), di-(2-ethylhexyl) phthalate (DEHP), diethyl phthalate (DEP), di-isodecyl phthalate (DiDP), di-isononyll phthalate (DiNP), di-*n*-hexyl phthalate (DnHP), and di-*n*-octyl phthalate (DnOP). Among the eight phthalates compounds, diethyl phthalate (DEP) is the most prevalent, and this report mainly focuses on comparing greener chemical alternatives to this representative phthalate compound.[21]

As phthalates are not chemically bound to the materials they are added to, they are released into the environment over time throughout the entire life cycle of a product. This can occur through heat, agitation, and prolonged storage of materials containing phthalates, resulting in environmental contamination. The released phthalate particles in the air and on phthalate-containing materials result in many routes of human exposure, including ingestion, inhalation, skin absorption, and intravenous injections. Studies on human exposure to phthalates and phthalic acid esters found that exposure levels can be up to 70 micrograms/kilograms/day.[2] In addition, DEHP (Bisphthalate) and DiNP (Diisononyl phthalate) have been found to be ecologically persistent, with a half life in water of around 360-900 hours.[3]

The effects of plastic pollution and phthalate release from those plastics over time are compounded into accumulation of phthalates in the environment, the biologic effects of which have been studied for both wildlife and humans. For wildlife, exposure to phthalates can cause developmental and reproductive disturbances, including reduced number of offspring and decreased hatching success rate. Even though phthalates are not classified as persistent chemicals, recent data from surface waters have observed higher than normal concentrations of phthalates present. More concerningly, phthalates are proved to bioaccumulate in organisms, with higher bioaccumulation factors in invertebrates than that in vertebrates. Investigations on annelids and molluscs have shown that exposure to phthalates could lead to mitotic inhibition, abnormal chromosomal activity, and delayed larval development. Although only low acute toxicity of phthalates is observed on terrestrial environments and organisms, soils could hold much higher concentrations of phthalates, meaning regulations and precautionary measures should still be taken to prevent further environmental contamination from phthalates. In fish, phthalates are shown to affect steroid biosynthesis and metabolism; similarly, in mammals, phthalate exposure is related to altered enzyme expressions and activities in the synthesis and metabolism of sex steroids.[15] The mechanism of phthalate interference with steroid hormones lies in the structural similarity between the phthalic benzene ring and the steroid A ring, which allows phthalates to bind to the active site of steroid receptors. The specific interactions, either agonistic or antagonistic, between phthalates and nuclear receptors (NRs) of steroid hormones are largely determined by the size of phthalic side chains.[23]

Phthalates can enter the human body through various routes such as inhalation of contaminated indoor air and household dust, ingestion via diet, skin contact with personal care products containing phthalates, and transfer from mother to fetus during pregnancy.[24] Generally, at low exposure levels, phthalates could be metabolized by human bodies through a two-step metabolic pathway. In phase one, lipases and esterases catalyze the hydrolysis of diester phthalate into monoester phthalate metabolites, which predominantly occurs in the intestine and parenchymal regions. Subsequently, these monoester phthalates undergo phase 2 conjugation facilitated by uridine 5'-diphosphoglucuronyl transferases, leading to the formation of glucuronide conjugates that are easily excreted out via urine. It is important to note that the metabolic pathways differ between short-branched and long-branched phthalates. Short-branched phthalates, such as dimethyl phthalate (DMP) and diethyl phthalate (DEP), can be directly excreted in urine following phase one transformation into their monoester phthalate forms. Conversely, long-branched phthalates, including butylbenzyl phthalate (BBzP), Di(2-ethylhexyl) phthalate (DEHP), and Di-iso-nonyl phthalate (DiNP), requires several biotransformations such as hydroxylation and oxidation in the two-step metabolic pathway before being successfully excreted out of the human body. However, what is of concern is the increased bioactivity observed in monoester phthalates - the supposedly detoxified metabolites of hazardous phthalates, proven by both *in vitro* and *in vivo* studies.[22]

There are many health effects linked to phthalate exposure, mostly due to the endocrine disrupting activity of phthalates. Although phthalates are metabolized and do not bioaccumulate in the human body, their metabolites are known endocrine disruptors. One such metabolite is mono(2-ethylhexyl) phthalate (MEHP), which has been found to cause reproductive dysfunction in animals studies.[3] While there is still limited understanding of its pathophysiology, *in vitro* studies have also found a positive association between exposure to phthalates and their metabolites, and endometriosis.[4] As potent endocrine disruptors, phthalates also pose a significant risk during prenatal exposure, which can greatly impact neurodevelopmental and neurobehavioral outcomes in children.[24] Since phthalates have specifically been shown to disrupt androgen homeostasis, people at key developmental stages of life are especially at risk to exposure: pregnant women, infants and toddlers, and pubescent children.[5] Many studies have shown that exposure to phthalates can lead to decreased testosterone levels. Studies in rats have revealed that dosing the pregnant mother with phthalates could cause its offspring to suffer from defects in the male reproductive tract. Similarly, studies on humans have also demonstrated the anti-androgenic effects of phthalates on development of the male reproductive tract.[23] Phthalates are also capable of crossing the placenta so transgenerational toxicity due to fetal exposure is another major health issue.[5] In general, the hormonal imbalances associated with phthalates negatively affect adiposity, puberty, and neurodevelopment.[6] More specifically, human epidemiology studies have found that phthalate exposure is correlated with type II diabetes and insulin resistance, overweight/obesity, allergy, and asthma.[8] Rodent studies have also found other adverse effects on reproduction and development such as increased prenatal mortality, reduced growth and birth weight, skeletal, visceral, and external malformations.[7]

Phthalates and other chemicals found to disrupt the endocrine and reproductive system have been observed in higher levels in women of color linked to exposure from these beauty products.[9] The requirement of women of color to conform to a certain beauty standard has led to women of color being more exposed to these chemicals compared to white women, regardless of their socioeconomic status. Workplace exposure is another avenue by which women of color are exposed due to their high levels of employment in the beauty industry.[10-11] The aforementioned effects of phthalates then go on to disproportionately affect the women using these products who are often left without market alternatives.

While there is yet to be a comprehensive understanding of the risks associated with phthalate exposure, the extensive use of phthalates in the manufacturing of so many widely used products is a major public health and environmental issue. The current results from ecological, animal, and epidemiology research alone suggest that it is imperative to find a safer alternative for phthalates. In response to research findings on the potential health risks associated with phthalate exposure, regulatory measures have been implemented. The National Toxicology Program (NTP) expressed concerns in 2006 regarding the adverse effects of phthalates, particularly DEHP, on male infant reproductive tract development. In 2008, the Consumer Product Safety Improvement Act (CPSIA) restricted the use of three phthalate compounds, namely DEHP, DBP, and BBP, in toys and childcare articles at concentrations exceeding 0.1%. Subsequently, in 2017, the final phthalates rule was put in place by CPSIA, which permanently prohibited the use of these three phthalates in childcare articles. In 2018, the FDA banned 26 phthalate compounds as food additives and food-contact materials. The most recent regulatory development involves the FDA reopening the comment period to gather safety information on the remaining phthalates authorized for use as plasticizers in food-contact applications. These regulatory measures reflect the need to minimize potential health risks associated with phthalate exposure and underscore the importance of continued research on this topic.[25-26]

This report will focus on identifying and analyzing a number of alternatives specifically for the fragrance stabilization properties of phthalates. For this use of the chemical, it is commonly found in cosmetics and personal care products that disproportionately expose women, and especially women of color. Additionally, although the EU has banned many phthalates (DiPeP, DnPeP, PIPP, and DMEP) in consumer products, regrettable substitutions and lack of regulation in the US are still issues that we hope to address in our project.[12]

Approach

Our goal is to improve the safety of hair relaxers, either by removing or discovering a safe alternative to phthalates. To do this, we first needed to understand the role of phthalates in personal care products. While their mechanism of action remains ambiguous, it is known that phthalates play a role in stabilizing fragrances in care products, a feature that many consumers of cosmetic products value. We conducted an evaluation of the harmful impacts that phthalates may pose to humans and the environment, which include but are not limited to bioaccumulation in fish, endocrine disruption in humans (disproportionately affecting women of color), and aquatic toxicity. These are such effects that we hope to eliminate in any proposed alternatives.

We then proceeded to research possible alternatives to phthalates. Our criteria was such: we looked for decreased health hazards, scent stabilizing capabilities, reduced environmental impact, performance effects on the product itself (time to relax hair and length of treatment), and economic feasibility with respect to phthalates (cost and manufacturing considerations). We decided to research alternatives to phthalates in products where they served as plasticizers and conducted an extensive review of scientific literature and patents, and asked the question of whether or not it would be viable to repurpose such alternatives in hair relaxers. We began with 11 initial candidates, which were chemicals with scent stabilization abilities that did not require additional stabilization. Our sources of inspiration were naturally occurring compounds with intrinsic scent such as vanilla or essential oils, biological scents like skunk spray, chemicals used in the food industry such as antioxidants and preservatives, and novel green technologies like encapsulation.

Next, we evaluated all proposed alternatives according to the metrics outlined above. Additionally, we constructed a hazard table as a means of ensuring that we considered all toxicity effects that the alternatives may have, indicating toxicity level for each hazard category. We used Pharos to view compiled results from authoritative lists, and conducted deeper literature review via PubChem and CAS Common Chemistry. All viable alternatives needed to either meet or exceed the performance and health metrics of phthalates in hair relaxers. Finally, we narrowed down our solutions to the best ones, along the guiding principles of minimizing relevant health hazards to humans and the environment, choosing well studied chemicals, and looking for technical feasibility for formulation use as indicated by existing industry usage, as well as good metrics in scent stabilization capabilities.

Table 1. Hazard table of the 11 initial phthalate alternative candidates

	Group I Human Endpoints			Group II and Group II* Endpoints			Ecotoxicity	Fate	Physical Hazard
Common name or trade name	**Carcinogenicity, Mutagenicity Toxicity**	**Developmental and Reproductive Toxicity**	**Endocrine Activity**	**Acute Mammalian Toxicity, Systemic Toxicity, Neurotoxicity**	**Skin Irritation/Corrosivity**	**Eye, Respiratory Irritation/ Sensitization**	**Aquatic Toxicity Acute/chronic**	**Persistence Bioaccumulation**	**Reactivity, flammability**
2-Methylquinoline	DG	DG	DG	M	DG	H	DG	DG	M
Vanillin	DG	DG	DG	M	P	M	M	DG	DG
Benzyl Benzoate	P	P	DG	M	P	DG	H	P	DG
Octylphenoxy-ethanol	P	P	H	M	H	vH	vH	P	DG
ascorbic acid	DG	DG	DG	DG	DG	H	DG	P	DG
1,2-benzopyrone (Coumarin)	M	P	DG	H	H	P	M	P	DG
Dipropylene glycol	DG	M	DG	P	P	H	DG	P	DG
Propylene glycol	L	L	H	L	DG	L	L	vL	L
Cellulose nanocrystals (Beta Glucose)	L	L	DG	L	L	L	L	vL	M
tocopherol	DG	DG	DG	DG	P	DG	DG	P	DG
Acetic Acid	DG	M	DG	M	DG	H	DG	DG	M
Diethyl Phthalate	P	P	H	M	H	M	H	vH	DG

Key
Data Gap
Potential Concern
Very Low
Low
Medium
High
Very High

Strategy 1: Coumarin

Inspiration

Coumarin is a heterocyclic compound that was first isolated from *Dipteryx Odorata* Willd, also known as Tonka beans and sweet clover, is widely available in plants from 600 genera and 100 families.[10] Coumarin is not exclusive to the Tonka beans, and has been found in other edible fruits such as strawberries, apricots, and cherries. The synthetic pathway of coumarin was first discovered by William Henry Perkin through a series of carbon to carbon condensations later known as the Perkin reaction. Ever since its discovery, coumarin has been used heavily in the perfume industry due to its distinct scent stabilizing character. The flavoring strength of coumarin is three times that of vanillin per unit weight. Its low volatility in addition to its vanilla-like aroma allowed coumarin to stand out in the competition.[11] Coumarin, on the other hand, could be found in many medicinal plants and was shown to be thermally stable, allowing it to endure heat during the fragrance production process.[12] Furthermore, coumarin's therapeutic properties include anticancer applications mitigating the effects of radiotherapy while also being used in formulation to treat prostate cancer, renal cell carcinoma, and leukemia.[10] However, since 1954, coumarin was banned in all food products due to its toxicity to animals and the severe liver damage caused by low dosage. Coumarin's heterocyclic structure and function is similar to that of phthalates with both containing aromatic phenolic rings and an carboxylate/ester-like functional group, while mitigating some off-target effects of phthalates, provides a great bio-inspired chemical to be a functional alternative. Current technologies of fragrance utilizing coumarin are promising like photocontrollable release which liberate coumarin based fragrances to act as a scent (less-bioaccumulation).[13]

Technical performance

Coumarin has been demonstrated to have good technical performance as a fragrance ingredient in hair care products and can be utilized as a viable substitute for phthalates. The sweet, vanilla-like scent of coumarin makes it a popular top note in perfumes.[11] It can offer a nice scent that can help cover up any unappealing smells from other components when used in hair care products. Another benefit of coumarin is that it can improve how well other smells work in a product. It can aid in stabilizing and extending a product's aroma, extending its duration on the hair, crucial in an environment that has constant exposure to water and air.

Coumarin has a low vapor pressure of 0.00098 mm Hg at 25℃ which makes coumarin a useful scent fixative.[17] In conjunction with coumarin's natural vanilla scent and its viability as a fixative, coumarin is mostly used with other scents such as lavender, rosemary, citrus oils, and oak moss to stabilize and prolong these scents. The ability of coumarin to both produce its own scent and stabilize other scents makes it a promising alternative to phthalates, whose main purpose is as a fragrance stabilizer.

As coumarin is a white crystalline powder, it is important to take into consideration the solubility. Coumarin's partition coefficient is at 1.39 signaling a preference for organic solvents such as oils, ethanol, ether, and chloroform. It is soluble in water (see Table 2) but to a much lower extent. It is noteworthy that it is soluble in water at higher temperatures, however this may pose a challenge during formulation. The stability of oil in water emulsions used in hair care products was found to be increased with the addition of coumarin in the product. This led to a decrease in propensity for the oil and water phases to separate, and lengthening the product's shelf life.[16]

It has also been shown that coumarin contains antibacterial qualities that could be useful in hair care products. According to research in the Journal of Applied Microbiology, coumarin is effective against a number of species of bacteria that are frequently found on the scalp, indicating that it might be helpful in preventing scalp infections.[17] Other research has shown that high concentrations of coumarin may lead to alopecia, so concentration and formulation is key.

Coumarin can be utilized as an excellent technical substitute for phthalates and has good technical performance as a fragrance ingredient in hair care products. Manufacturers looking for safer substitutes for conventional perfumes will find it to be an appealing option due to its capacity to produce a pleasing scent, improve fragrance performance, and be soluble.

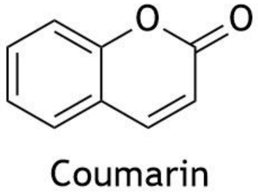


Figure 1. Coumarin

Table 2. Coumarin's Chemical and Physical Properties

Chemical and Physical Properties	
Empirical Formula	$C_9H_6O_2$
Molecular Weight	146.14 g/mol

Boiling Point	297℃
Density	0.935 g/cm^3 @ 20℃
Vapor Pressure	0.00098 mm Hg @ 25℃
LogP	1.39
Solubility in Ethanol	29 mg/mL@ 25℃
Solubility in Water	1.7 mg/mL@ 25℃

Health and environmental performance

As phthalates are a major concern with endocrine activity, it is equally vital to investigate it during the performance review. There is no recorded endocrine activity.[14,19] In moderate concern, there is neurotoxicity and carcinogenicity, however these are reported with low confidence. However, the majority of tests for mutagenic and genotoxic potential suggest that coumarin is not a genotoxic agent. This includes in vivo studies with *Drosophila melanogaster* and mouse micronucleus tests. The threshold remains at over 4500 times the estimated human exposure from the diet and from fragrance use in cosmetic products[18]. This does, however, show that there is a threshold at which coumarin induces toxicity and carcinogenicity. There is potential concern with reproductive toxicity, centered around damaged fertility or damage to an unborn child. There is high acute mammalian toxicity, mainly through oral ingestion. This does, however, require high doses. Along this same route, there is low hepatotoxicity concern in patients given a high dose of about 50-7000 mg/day.[19] Target organs for toxicity and carcinogenicity in the rate and mouse are primarily the liver and lung.

This project focuses on phthalate alternatives for hair relaxers making skin and eye sensitization and irritation a major concern. Initial scans of coumarin indicate a high concern for these criteria. However, a careful review of literature reveals that coumarin is generally considered to be a weak skin sensitizer. The No Expected Skin Induction Level as set by the Research Institute for Fragrance Materials is 3.500 mg/cm^3, a safe level for most people except a small minority, 2 in a study of 300 subjects. These people were then seen to have an allergic reaction to coumarin rather than a toxicity reaction.[18,19]

Coumarin readily biodegrades, and at 28 days its aquatic presence has been reduced to 92.7%. Similarly, an EPI Suite analysis showed that coumarin is not persistent and does not bioaccumulate. Coumarin has significantly less of an impact than other phthalates studied.

Estimated exposure from fragrance use in cosmetic products has been estimated to be 0.02 mg/kg/day. There have been no reported adverse effects of coumarin in susceptible species in response to doses which are more than 100 times the maximum human daily intake. It is also important to note that all of these studies for reproductive toxicity, neurotoxicity, carcinogenicity, and hepatotoxicity concern relied on oral consumption of coumarin to the animal test subject dissolved in water. It is therefore also reasonable to assume that in a salon setting with professional assistance the product would not be ingested orally. There is more concern if the product were to be made available for at home application where there is a possibility of younger children accidentally ingesting the product.

Strategy 2: Dipropylene Glycol

Inspiration

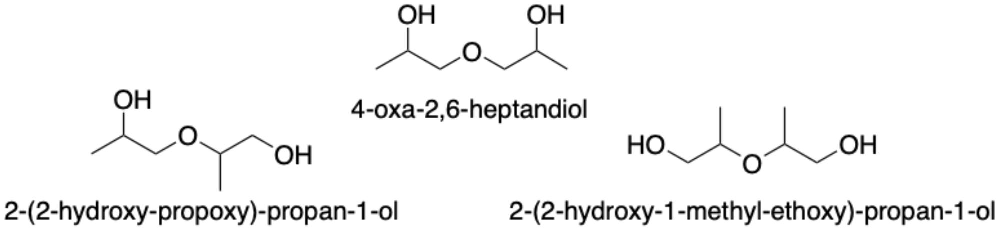


Figure x. Three isomeric compounds that make up dipropylene glycol

Dipropylene glycol, or DPG, is an odorless, colorless liquid that consists of a mixture of 3 isomeric compounds (Figure x). It currently has a diverse range of uses across different industries, including as a solvent, plasticizer, polymerization initiator, and chemical intermediate.[32] However, the widespread use of DPG in perfume formulations and the fragrance industry is what inspired an in-depth exploration of its potential as a phthalate alternative.

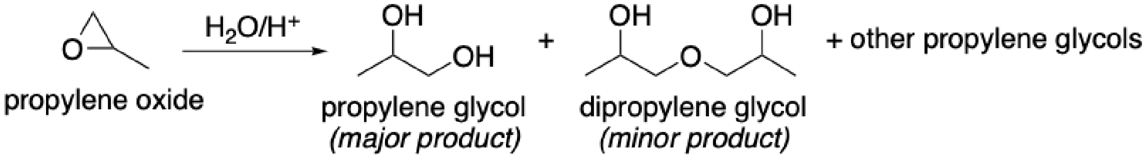


Figure x. Reaction scheme for production of propylene and dipropylene glycol

DPG is primarily produced as a byproduct of the propylene glycol manufacturing process, which involves acid catalyzed hydrolysis of propylene oxide following the reaction scheme illustrated in Figure x.[34] Propylene glycol itself has been labeled as GRAS (generally regarded as safe) and is often used as a FDA approved indirect food additive.[34] It shares many similar properties and industrial applications with dipropylene glycol, and was investigated accordingly as an initial candidate alternative. However, DPG was found to both have more potential as a scent stabilizer and have lower associated endocrine disruption hazards (Table 1). DPG is also already used as an additive in cosmetics, skin care, and hair care products, where it serves many purposes. The main use of interest is DPG's scent stabilizing properties, but within a formulation, DPG also acts as a solvent and humectant, improves texture through decreasing viscosity, and masks unpleasant smells from other active ingredients.[35] We interpreted this versatility as an indicator that this chemical was a promising alternative to phthalates worth investigating.

Technical Performance

To be a viable alternative for phthalates in a hair relaxer formulation, the proposed solution must have comparable technical performance to that of the original chemical. Dipropylene glycol demonstrates high scent stabilizing properties, which was the main performance metric focused on for this project. In addition, DPG performs well in terms of other technical properties important for personal care product formulation, such as shelf-stability, compatibility, and solubility.

DPG's mechanism of action for stabilizing scent in fragrance products is through its function as a fixative. In perfumery, ethanol is the main carrier used for perfume oils due to its excellent solvent properties, but has a low boiling point and evaporates quickly to release fragrance molecules into the air.[36] To combat ethanol's fast evaporation, fixatives are needed to equalize the different vapor pressures of all the elements in a perfume formula [39]. These fixatives are usually substances with low volatility to balance out high volatility components such as ethanol, and have the effect of slowing down the rate of evaporation of fragrance molecules. This in turn increases the tenacity, or lasting ability, of the perfume. As reported in Table 3, DPG has a high boiling point and a relatively low vapor pressure, both of which are indicators of low volatility, signifying high scent stabilization performance. DPG's boiling point is comparable to that of diethyl phthalate (295°C), and while DPG's vapor pressure is an order of magnitude higher than diethyl phthalate (0.002 mmHg),[41] it is still small enough to provide sufficient fixative performance.

Table 3. Chemical and Physical Properties of Dipropylene Glycol

Molecular Formula	$C_6H_{14}O_3$
Molar Mass	134.17 g/mol
Boiling Point	231.9°C [43]
Vapor Pressure	0.0021 kPa (0.016 mmHg) at 25°C
Density	1.0206 g/cm^3 at 20°C [43]
Solubility	Miscible with water, soluble in ethanol
Stability	Stable, combustible, incompatible with strong oxidizing agents.[32]

Other chemical and physical properties relevant for product formulation are summarized in Table 3. Being miscible with water is an especially important property for the technical viability of this solution, since hair care products are often aqueous solutions or oil-in water emulsions. The water miscibility that DPG demonstrates is definitely a strong point since it outperforms diethyl phthalate, which has low water solubility (1.08 mg/mL). DPG itself also possesses great solvent properties for various organic compounds used in the formulas of hair care products. DPG is stable during transport and not reactive with water or common storage materials, only reacting vigorously with acids and strong oxidizing agents.[32] This mainly low chemical reactivity is desirable for the shelf-stability and compatibility of DPG with other common active ingredients in hair relaxers.

Unfortunately, the reactivity with strong oxidizing agents is a major limitation of using DPG as a phthalate alternative in hair relaxers. Of the various types of hair relaxers, no "lye" or thio-based formulations use the reducing agent ammonium thioglycolate to break disulfide bonds in the hair, and require a neutralization step after the relaxing treatment.[45] This neutralization step involves using an oxidizing agent, which can be incompatible with DPG. This issue could potentially be resolved through careful formulation or only using DPG in the treatment solution, but this incompatibility is a factor to consider when investigating dipropylene glycol for use in hair relaxer formulations. Regardless of this pitfall, dipropylene glycol demonstrates promising technical performance on many other fronts as a phthalate alternative in personal care products.

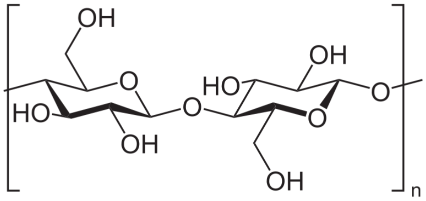
Health and environmental performance

Dipropylene glycol is expected to present a low hazard to the environment due to it preferentially partitioning into water. It has a low soil sorption coefficient, meaning that it will likely mobilize and will not adsorb onto particles. The compound is also not volatile due to its low vapor pressure and high solubility in water. Photodegradation by light is not predicted, but it can be degraded under aerobic conditions by bacteria in soil and water. Most importantly, dipropylene glycol is not expected to accumulate in aquatic organisms, presenting a much lower environmental hazard than phthalates (based on data from fish, amphibians, and bacteria). Duration lasts anywhere from 18-48 hours.

Dipropylene glycol is not acutely toxic by oral, dermal, or inhalation exposure. It is slightly irritating to the skin and eyes, which may be of concern in a hair relaxer formulation. However, it has a low potential to produce allergic skin reactions, based on a human clinical study (Johansen *et. al*, 1995). There are no explicit studies on propylene glycol carcinogenicity, but based on data from propylene glycol (to which dipropylene glycol is rapidly converted), it is not expected to be carcinogenic. Similarly, studies were conducted on tripropylene glycol and propylene glycol and showed no signs of reproductive toxicity.

Strategy 3: Cellulose Nanocrystals

Inspiration



Cellulose Nanocrystals have been found to be isolated from cellulose that has been synthesized through acid hydrolysis, dialysis, and vacuum filtration to obtain its cyclic and polymeric form.[31] It was first produced in 1947 by Nickerson and Habrle utilizing cellulose, sulfuric/hydrochloric acid at boiling temp, and degrade less ordered regions in order to synthesize cellulose nanocrystals (CNC for short).[31] With these methods of synthesis, the inspiration comes from mass producing cellulose and what methods/options are available for this supply; moreover, taking a deeper dive into mass production of cellulose, cellulose is found to be in numerous different sources like plants (especially in wood pulp and cotton fibers), algae, bacteria (Komagataeibacter xylinus), Tunicates (within animals utilizing enzyme complexes that are within the epidermis membrane).[33] It is also synthesized in an additional alternative method through the grinding and acidification of discarded industrial hemp.[37] Cellulose nanocrystals can carry out a myriad of functions with being a fragrance release system, being utilized as a nanofiller in past projects within the green chemistry class, and being versatile or readily available from most types of plants.[40] Furthermore, CNCs provide inspiration and promising evidence that it could replace phthalates as a scent stabilizer and could be an alternative fragrance delivery method like a scent carrier instead.

Its current use in formulations provide insight into why we chose this bio-inspired alternative in addition to what was stated beforehand. CNCs are being currently used in formulations that are in makeup removers, moisturizers, and cleansers.[42] It also performs the function of a humectant that locks in moisture to prevent that thick but non-tacky feel and is used in healing modalities like balms or lotions.[42] With the increased and modified functional use of cellulose nanocrystals can perform a multitude of functions in formulations in personal care products and can provide a great alternative than phthalates.[42] Instead of mimicking the function of phthalates, providing an alternative function that changes the mechanism can have its benefits.

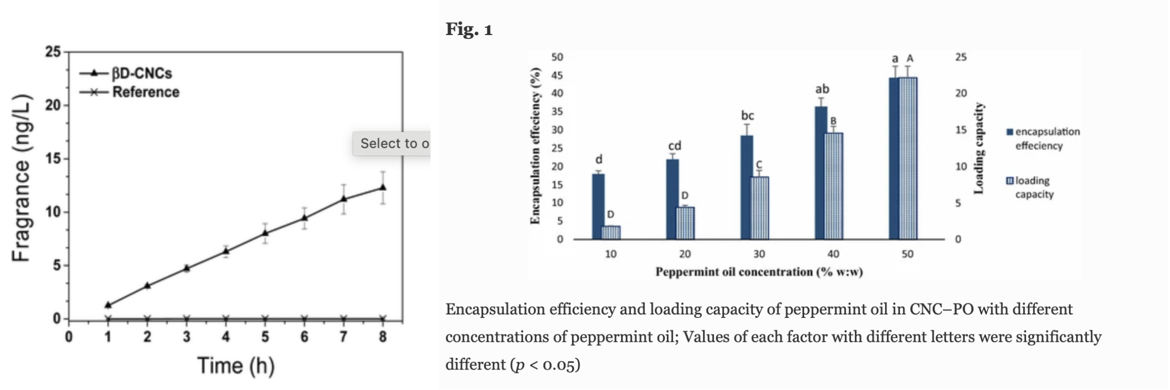
Technical Performance

With the technical performance of phthalates, we wanted to make sure that our alternative does not contain the harsh side effects of phthalate performance on the body and the environment while also simultaneously keeping in mind the function of phthalates in stabilizing scent. Instead of just stabilizing the scent, we can utilize a specific polymer to be conjugated onto a specific scent molecule to perform a "stabilizing-like" feature of a scent; moreover, we found an alternative that would go into a change in this stability and become a carrier of the scent instead. Cellulose nanocrystals are a great alternative because its proposed mechanism is similar to that of vesicles within the body.[40, 44] Similar to some labs on campus (like the Matt Francis Lab), vesicles are used to deliver drugs into cells utilizing endocytosis.[46] However, cellulose nanocrystals performs a similar function but instead of doing drug-delivery in this case, there is evidence to suggest that when the fragrance molecule is conjugated to its hydroxyl within this cyclic polymer of CNC, it can be used to deliver fragrance instead of drugs. In this case, when the CNC molecule is attached to surfaces, it allows for scent to be released when the cyclic polymer is opened.[44] When the molecule is conjugated onto the Cellulose nanocrystal's large surface area and abundant surface hydroxyl group is utilized for modifications more for hydrophilic properties and oil or water emulsion properties. Based on its structure, it can form strong hydrogen bonding because of its availability of hydroxyl groups.

Cellulose nanocrystal's technical performance is different to that of diethyl phthalate with key distinguishing characteristics. According to table 4, cellulose nanocrystals has a molecular weight of 370.35 grams/mole, a melting point of 260.1 degrees Celsius, vapor pressure of 0 mmHg, has an insoluble and hydrophobic miscibility in water or hydrophilic solvents, and has a density of 1.27-1.61 kilograms/liter.[47, 48] Diethyl phthalate has a a molecular weight of 222.24 grams/mole, a melting point of -2.78 degrees Celsius, a vapor pressure of 1 at -2.78 degrees Celsius, has a miscibility with water at less than 1 mg/mL at 18.9 degrees Celsius, and has a density of 1.12 at 20 degrees Celsius.[47, 48] Comparing these metrics, the molecular weight is higher for cellulose nanocrystals indicating that a trade off is going to be needed to balance out the weight in the formulation, especially considering that in fragrance that the molecules are airborne when sprayed out of the bottle.[47, 48] Additionally, recognizing that the melting point is increased for cellulose nanocrystals indicates that its shelf life stability is great and would not just separate out of the product when put at higher temperatures, or lasts longer than diethyl phthalate at higher temperatures.[47, 48] The vapor pressure is decreased which is a good thing because the decreased amount of vapor pressure indicates a lower volatility.[47, 48] However, with its miscibility, cellulose nanocrystals would work best in an oil based formulation rather than a water based formulation.[47, 48] Finally, its density is the same as diethyl phthalate, so it would not separate as easily when sitting on the shelf for a long period of time. A few concerns are that it is flammable and is an asthmagen for high periods of use. In addition to this information, release of fragrance metrics and encapsulation efficiency are shown within figure 5 to compare the max encapsulation efficiency and release over time.[49]

Table 4: Cellulose Nanocrystals Cross-Comparative Analysis with Diethyl Phthalate

	Cellulose Nanocrystals	Diethyl Phthalate
Molecular Weight (grams/mol)	370.35	222.24
Melting Point (degrees Celsius)	260.1	-2.78
Vapor Pressure (mmHg)	0	1 @ -2.78 degrees Celsius
Miscibility	Insoluble/Hydrophobic	Less than 1 mg/mL at 18.9 degrees Celsius
Density (kg/L)	1.27 - 1.61	1.12 @ 20 degrees Celsius



Encapsulation efficiency and loading capacity of peppermint oil in CNC–PO with different concentrations of peppermint oil; Values of each factor with different letters were significantly different ($p < 0.05$)

Figure 5: Release of Fragrance and Encapsulation Efficiency Capacity of Fragrance

Health and environmental performance

A comprehensive ecotoxicological evaluation of cellulose nanocrystals was conducted by Kovacs *et. al* (2010), testing rainbow trout hepatocytes and nine different aquatic species. Using acute lethal toxicity testing, where the concentration required to cause a lethal effect was measured, they demonstrated that acid-hydrolyzed cellulose nanocrystals were practically non toxic. They confirmed these findings in whole organisms where effects occurred at concentrations >100 mg/L. Comparing CNC's to a known cellulosic material, carboxymethyl cellulose, similar threshold concentrations were found, indicating minimal concern for CNC's toxicity. In addition, CNC's were shown to be 1,000 to 10,000 fold less toxic than titanium dioxide and fullerene, indicating low aquatic toxicity potential.

Findings published by O'Connor *et. al* (2014) indicated nontoxicity to aquatic organisms and mammals. Additionally, the fibers of CNC's are too small to be bio-persistent in the lungs. They are both dispersible in water and biodegradable. CNC's also present low risk for carcinogenicity and mutagenicity, reproductive and developmental toxicity, neurotoxicity, skin, respiratory, and eye sensitization, and low flammability, though data gaps do exist for endocrine activity.

Recommendations

The extensive nature of this report is evidence that a landscape for phthalate alternatives in hair care products not only exists, but has the potential to reshape the industry as we know it. However, it is important to acknowledge that these alternatives have their own drawbacks, some which are still unidentified.

Coumarin, a white crystalline powder, is used in the fragrance & cosmetic industries. Its sweet vanilla-like scent masks unpleasant smells and enhances other fragrances, extending their duration on the hair. Coumarin's solubility in water simplifies formulation and reduces the risk of accumulation or irritation. It also improves the stability of oil-in-water emulsions, prolonging shelf life. Additionally, coumarin exhibits antibacterial qualities that can help prevent scalp infections. Compared to diethyl phthalates, it has less aquatic toxicity. However, Coumarin has high skin and eye sensitization, and high acute mammalian toxicity. It has data gaps in endocrine activity. While Coumarin has many attributes that position it to be a good alternative, the skin sensitization coupled with data gaps in endocrine activity make it challenging to implement.

Dipropylene glycol (DPG), a color & odorless liquid, is found often used as a plasticizer, solvent, and scent stabilizer. Currently, it is used in the perfume & personal care industries. It demonstrates high scent stabilizing properties and performs well in terms of other technical properties important for personal care product formulation, such as shelf-stability, compatibility, and solubility. However, its reactivity with strong oxidizing agents limits its use in some hair relaxer formulations. Despite this limitation, DPG shows promise as a phthalate alternative in personal care products.

Cellulose nanocrystals (CNC) can be isolated from various sources such as plants, algae, bacteria, and industrial hemp. They can function as fragrance releasers, scent carriers and other roles. Despite being first produced in 1947, CNC's have not been well studied. CNCs could be conjugated onto scent molecules to stabilize them, or serve as a carrier of scent. CNC has a high molecular weight and melting point, low vapor pressure, is insoluble and hydrophobic, and has a density similar to that of diethyl phthalate. However, it would work best in oil-based formulations and is flammable and an asthmagen with prolonged use.

Another factor to take into account is the financial costs behind implementing these alternatives. While CNC can be derived from cheap alternatives, it needs to be significantly more researched which may cost a large amount of money. Currently CNCs cost around $50/kg which is significantly higher than both coumarin and DPG which are at $10 and $18 per kg respectively.

The three alternatives presented have unique backgrounds all while accomplishing the task set out: finding safer alternatives to phthalates. Coumarin and DPG, are relatively well studied and already used in industry, while CNCs are novel and not common in industrial use cases. While all three alternatives should be researched more thoroughly, we believe that CNCs have the most potential due to their novelty, bioinspired design, and eco-friendly synthesis.

Name	Hazards	Cost	Feasibility
Coumarin	Medium	Low	High
DPG	Medium	Low	High

CNC	Low	High	Medium

Remaining questions

The effects of long-term exposure of phthalates on populations have remained a knowledge gap. Most studies available now focused on the effects of limited species within the invertebrate phyla. However, sensitivity towards phthalates could vary drastically across species. More research should be done by sampling from different species for a holistic view of phthalate toxicity on the entire phylum. Moreover, cross contamination of different plasticizers could potentially lead to mixture effects, reinforcing the toxicity of each individual chemical. The potential adverse effects on the health of wild aquatic populations requires further research. Low dosage of phthalates is yet to be proven to have an adverse effect on fish and other aquatic life. However, the potential effect of high concentrations of phthalates in water bodies still remains a concern. Studies have also shown that phthalates could have multiple interaction sites within the body. However, the mechanism of action at each site remains unknown. Further research is needed to fully understand the pathways of phthalates in order to access the biological effects and organismal vulnerability.[15]

In terms of health and environmental concerns, all three of our proposed alternatives demonstrate promising potential as greener solutions to the issues of phthalates. Nevertheless, their feasibility remains unclear. A potential limitation with coumarin relates to its solubility in hair relaxer formulations. Due to its low solubility in water, potential products with coumarin could face difficulties in creating water-based formulations as well as in ensuring even application of the product onto hair. Cellulose nanocrystals (CNCs) represent a relatively novel compound for use in cosmetic and personal care products. Their monomer form, glucose, has been widely studied and used for several decades, without presenting any hazardous properties. However, the hazards associated with the polymer of CNCs require further research, particularly when applied in personal care formulations. Furthermore, the effect of scent molecule size on the performance of CNCs has yet to be revealed in scientific literature.

Our Team

Giselle Arroyo Torres is a 4th year in the B.S. Chemical Biology program at UC Berkeley with a minor in Toxicology. Through an interest in sustainability and public health, she will be focusing on the hazards of proposed compounds.

Claire Li is a 3rd year majoring in Chemical Biology at UC Berkeley's College of Chemistry with a minor in Bioengineering. She brings an understanding of chemical synthesis and mechanisms, as well as scientific research experience. She is interested in finding more sustainable and safe alternatives to harmful chemicals in personal care products, and will focus on finding bio-inspired solutions and characterizing their associated risks.

Elaine Liu is a 3rd year majoring in Chemical Biology and Economics at the University of California, Berkeley. With a chemistry background, she will be working on the chemical list in proposed strategies and identifying key properties that will lead to potential health and environmental impacts.

Kodi Nguyen is a 3rd year majoring in Molecular and Cell Biology with an emphasis in Neurobiology. He is currently an undergraduate student researcher in the Michelle Chang Lab. With a background in Neurobiology and Biochemistry, he will be focusing on toxicity of these chemicals and environmental impacts

Aarav Shah is a 2nd year majoring in Computer Science and Chemistry with a strong background in physical chemistry research, he hopes to leverage his strong problem solving skills to provide tangible & unique solutions to tackle the hazardous impacts.
Millie Wang is a 3rd year majoring in Economics and minoring in Chemistry with a background in pharmaceuticals and the life science industry. She will bring expertise on feasibility of proposed alternatives, taking into account regulatory processes (FDA approval) as well as cost and manufacturing.

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