Non-Petroleum Based Alternatives for Nail Polish Formulation

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Land Acknowledgment

We recognize that UC Berkeley sits on the territory of xučyun (Huichin), the original landscape of the Chochenyo-speaking Ohlone people, the successors of the sovereign Verona Band of Alameda County. This region continues to be of great importance to the Muwekma Ohlone Tribe and other familial descendants of the Verona Band. We recognize that every member of the Berkeley community has, and continues to benefit from, the use and occupation of this land, since the institution’s founding in 1868. Consistent with our values of community, inclusion, and diversity, we have a responsibility to acknowledge and make visible the university’s relationship with Native peoples. As members of the UC Berkeley community, it is vitally important that we not only recognize the history of the land on which we stand but also recognize that the Muwekma Ohlone people are alive and flourishing members of the Berkeley and broader Bay Area communities today.
About the Authors

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I. Executive Summary

Nail salon workers are highly exposed to toxic chemicals in the workplace that lead to increased rates of cancer, endocrine disruption, and reproductive and developmental toxicity. Many regulatory agencies, including the State of California Department of Toxic Substances Control (DTSC), are prioritizing removing toxic chemicals from cosmetics to improve conditions for these vulnerable workers. In response, cosmetic companies have been shifting away from using petroleum-based solvents and phthalates in nail polish formulations to meet regulatory and safety standards and improve overall worker health. This report considers safer alternatives to previously used “bad actor” chemicals in nail polish formulations. A zein-based formulation was found to have the biggest likelihood to introduce a new, vegan, clean-beauty alternative to the nail polish market that reduces toxic human health endpoints, with high potential to achieve similar performance to current nail polish formulations. Other strategies require technical performance modifications and additional toxicological research to be considered “safer” or “better” than what is currently in use.
II. Introduction

In recent decades, concerns regarding the health of nail salon workers have been raised due to high exposure to known toxicants in nail polish formulations. Nail polish formulations contain three key elements: a solvent, plasticizer, and film-former. The plasticizer increases flexibility and reduces cracking, the film former hardens the nail polish, and the solvent dissolves and dries the other materials for a smooth finish. The primary toxicants of concern in nail polish include toluene, formaldehyde, and dibutyl phthalate (DnBP). While reportedly phased out of formulations in the early 2000s, replacements for these chemicals still have toxic health endpoints. For example, toluene has a set Occupational Safety and Health Administration (OSHA) exposure limit. However, the majority of chemicals in nail polish formulations have no exposure limits or regulatory standards are outdated and inadequate for protecting workers. Additionally, many nail salon workers do not receive safe chemical handling training, as a result of a lack of implementation and enforcement by OSHA.

The California Department of Toxic Substances Control (DTSC) Safer Consumer Products (SCP) program works to identify hazards in nail polish products to minimize potential health and safety risks to nail salon workers. To reduce or eliminate exposure to toluene in nail salons, the DTSC has proposed listing toluene-based nail polish products on the California Code of Regulations ‘Priority Product’ list (Title 22, Division 4.5, Chapter 55), due to its potential to harm people or the environment. The State of California has also taken action to remove toxic chemicals from cosmetics, passing Assembly Bill 495 which will ban the use of phthalates and other harmful chemicals in cosmetics sold in California by 2025.

In response to the regulation of harmful chemicals in cosmetics, companies like L’Oreal are actively searching for safer alternatives that meet safety standards set by state and federal agencies, without compromising nail polish quality. As of 2021, Essie, L’Oreal's largest nail polish brand, as achieved formulations that are 100% vegan and “8-free,” meaning they are formulated without formaldehyde, toluene, dibutyl phthalate, formaldehyde resin, camphor, ethyl tosylamide, xylene, and triphenyl phosphate. However, there are still many chemical alternatives to consider to develop even safer nail polish formulations that require additional research and investigation. To address this issue, our team has partnered with L'Oreal and the DTSC to identify a range of non-petroleum-based alternatives to reduce and eliminate harmful chemicals in nail polish formulations. This challenge will ultimately address the need for safer chemical alternatives in nail polish formulations, and the implications of our findings can extend into other lacquer-based product formulations as well.

a. The Challenge

In partnership with the DTSC and L’Oreal, our team was tasked with completing the following:
1. Identify a range of non-petroleum-based chemical alternatives to existing chemicals used in nail polish formulations that have the potential to achieve comparable technical performance
   i. Consider alternatives that can be synthesized via non-petroleum-based starting materials
   ii. Evaluate the ability of the alternative to dissolve, plasticize, and form a film with other nail polish components
   iii. Consider comprehensive formulation changes that can improve performance in technical and environmental health areas

2. Determine a set of metrics to assess both technical performance and health performance and perform a chemical hazard assessment of all chosen alternatives

3. Synthesize findings and recommendations in a presentation and report that describes opportunities and constraints around implementation, health, and environmental impact and areas for further research

\textbf{b. Nail Salon Statistics and Worker Demographics}

A UCLA Labor Center Study found that there are approximately 23,745 nail salons in the US, 19% of which are in California\textsuperscript{8}. Most nail salons are mom-and-pop shops, and 92% of nail salons have fewer than 10 employees. However, more chains are starting to enter the market as report findings show that employment in the industry is expected to grow by 13% in the next decade, almost double the rate of other occupations\textsuperscript{8}.

The nail salon industry is primarily composed of immigrant (79%) women (81%) of reproductive age (65%), making nail salon workers especially vulnerable to adverse health effects of commonly used solvents. Additionally, many women in this industry are self-employed (30%) and working under low wages (80%), making them more likely to work long hours, increasing exposure duration. Studies have shown that cosmetologists and nail technicians have elevated rates of thyroid and lung cancer compared to the general population, suggesting that occupational exposure to toxic chemicals may be linked to adverse health outcomes\textsuperscript{8}.

A lack of regulatory measures protecting workers has only exacerbated these issues. Nail technicians often do not receive adequate information or training regarding chemical safety and are not provided personal protective equipment (PPE) to mitigate exposure to harmful chemicals in the workplace. Additionally, given the cost burden associated with basic equipment, nail polishes, and chemicals, workplaces often do not prioritize strict safety standards or lack appropriate ventilation to protect workers from chemical emissions\textsuperscript{8}.
c. The Three Key Components of Nail Polish Formulations

In this section, we outline the three primary components of nail polish formulations and describe which chemicals were previously and are currently used. The chemicals described will be characterized as “bad actor” chemicals in our search for safer alternatives. We define primary bad actor chemicals as phased-out chemicals with significant toxic health endpoints. We define secondary bad actor chemicals as those that have replaced primary bad actors in current formulations but still have moderate to high toxicity. The chemical composition of the described “bad actor” chemicals is summarized (Tables 1 & 2). A hazard assessment (Tables 3 & 4) was also performed to evaluate the toxic health endpoints associated with the bad actor chemicals. The methodology for determining hazard assessment scores is described in the following section, Health and Environmental Criteria.

Table 1. Solvent bad actors.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Molecular Formula</th>
<th>Molecular Weight (MW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>C(_7)H(_6)</td>
<td>92.14</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>C(_4)H(_8)O(_2)</td>
<td>88.11</td>
</tr>
<tr>
<td>Butyl Acetate</td>
<td>C(_6)H(_12)O(_2)</td>
<td>116.16</td>
</tr>
</tbody>
</table>

Table 2. Plasticizer bad actors.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibutyl Phthalate</td>
<td>Triphenyl Phosphate</td>
</tr>
</tbody>
</table>
Table 3. Hazard assessment of primary bad actor chemicals.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Carcinogenicity</th>
<th>Genotoxicity/ Mutagenicity</th>
<th>Reproductive Toxicity</th>
<th>Developmental Toxicity</th>
<th>Endocrine Activity</th>
<th>Systemic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>L</td>
<td>L</td>
<td>H</td>
<td>H</td>
<td>H - M</td>
<td>M</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>M</td>
<td>L</td>
<td>H</td>
<td>H</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

Table 4. Hazard assessment of secondary bad actor chemicals.

<table>
<thead>
<tr>
<th>Plasticizer</th>
<th>Carcinogenicity</th>
<th>Develop/ Reproduct Tox</th>
<th>Genotoxicity/ Mutagenicity</th>
<th>Skin/Eye Irritation</th>
<th>Endocrine Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di(ethylhexyl) terephthalate (DEHT)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>DG</td>
</tr>
<tr>
<td>Diisononyl hexahydrophthalate (DINCH)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Carcinogenicity</th>
<th>Develop/ Reproduct Tox</th>
<th>Acute/ Systemic Toxicity</th>
<th>Skin/Eye Irritation</th>
<th>Endocrine Activity</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butyl Acetate</td>
<td>L</td>
<td>M-L</td>
<td>M</td>
<td>H</td>
<td>DG</td>
<td>M-L</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>L</td>
<td>M-L</td>
<td>M</td>
<td>H</td>
<td>DG</td>
<td>M</td>
</tr>
</tbody>
</table>

*i. Solvent*

The solvent dissolves the various components of the formulation to combine into one formulation. Toluene is a clear, colorless, flammable, and volatile liquid that is a good solvent for organic compounds. Toluene is a petroleum-based, benzene derivative commonly used in paints and dyes, including nail polish. Nail salon workers are exposed to toluene by breathing in
vapor emissions, splashing it on their skin or in their eyes, or swallowing it, i.e. inhalation, dermal, and ingestion. Exposure to toluene can lead to neurotoxic effects and has been linked to birth defects after prenatal exposure (Table 3). Toluene has largely been replaced by ethyl and butyl acetate, our secondary bad actors. These solvents are linked to adverse health outcomes from occupational and environmental exposure due to their use in industrial coatings, adhesives, inks, and degreasers. The main route of occupational exposure to ethyl and butyl acetate is through inhalation, ingestion, skin and eye contact, targeting the eyes, skin, respiratory system, and central nervous system (Table 3). Short-term exposure to ethyl acetate has been shown to cause nose and throat irritation at concentrations above 400 ppm in 1.4 mg/L. In rare cases of exposure to ethyl acetate, it is shown to cause sensitization of the mucous membrane and eruptions of the skin. Overall, ethyl and butyl acetate pose fewer human health risks than toluene but still have many data gaps, particularly regarding endocrine-disrupting effects. Given our demographic of concern, we aim to evaluate whether these are viable alternatives.

**ii. Plasticizer**

In addition to a solvent, a plasticizer is needed to increase the durability of the nail polish by making it flexible and unlikely to crack when dry. Dibutyl phthalate (DnBP) is odorless and colorless to light yellow, oily, liquid used to make plastics soft and flexible. It is often found in raincoats, shower curtains, vinyl fabrics, and food wraps, but is also used in nail polishes and hairsprays. DnBP is listed as a substance of very high concern by the European Chemicals Agency (ECHA) regarding its links to reproductive toxicity and endocrine disruption (Table 4). Triphenyl phosphate (TPHP) is another plasticizer used in nail polishes, characterized as a colorless solid with a phenol-like odor. Studies have shown that the primary route of exposure to triphenyl phosphate for nail salon workers is dermal, although other routes of exposure may occur. Like DnBP, triphenyl phosphate has also been identified as a potential endocrine disruptor.

In the European Union, dibutyl phthalate and triphenyl phosphate are banned in cosmetics. Instead, chemicals including di(ethylhexyl) terephthalate (DEHT), diisononyl hexahydrophthalate (DINCH), and diisononyl cyclohexane-1,2-dicarboxylate, have been substituted. Minimal to no irritation has been observed with DEHT, and it is considered non-irritating and non-sensitizing to humans, however, it has been assessed as GreenScreen Benchmark 3. DINCH has been assessed as a GreenScreen Benchmark 2, indicating that safer substitutes should be considered. Moreover, there are significant data gaps for DINCH, which makes it hard to determine if it has any long-term health effects. Based on the study of biomonitoring of DINCH metabolites in pregnant women, there was no evidence of interference with the regulation of specific hormones required for pregnancy. Both of these chemicals (Table 4) are considered phthalates, which are being phased out of cosmetics. Our strategies present non-phthalate plasticizer alternatives.
iii. Film-Former

Lastly, the film-former, makes up most of the formulation and works to bind all of the components together by creating a film to suspend formulation materials. Most formulations use nitrocellulose, described as a liquid mixed with cotton fibers that have been ground small enough so that they cannot be removed. Nitrocellulose poses few risks to human health and is an excellent film-former. Moreover, Nitrocellulose is brittle and has poor adhesion properties, so it must be combined with other elements to create a good coating. Nitrocellulose will only be used to compare the technical performance of alternative film-formers, as health endpoints are not of concern.
III. Approach

a. Performance Criteria

Table 5 summarizes the performance metrics for the nail polish formulation as a whole as defined by our partners at L’Oreal. These metrics reflect a formulation that is easy to apply and forms a shiny and hard film once it dries in a reasonable amount of time. Once the formulation dries on the nail, it should last at least three days before it begins to crack or peel and be easily removed with existing nail polish removers. While testing the formulation is outside the scope of this project, these metrics were used as a guideline to identify the target properties of the film-formers, plasticizers and solvents.

Table 5. Summary of nail polish formulation performance metrics.

<table>
<thead>
<tr>
<th>Property</th>
<th>Measurement/Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film forming</td>
<td>Forms a film at room temperature</td>
</tr>
<tr>
<td>Gloss</td>
<td>&gt;60 GUs</td>
</tr>
<tr>
<td>Adhesion</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Persoz Hardness</td>
<td>Depending on the coat between 50 - 70</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Between 400-750 cP (shade dependent) using Brookfield viscometer spindle SC34</td>
</tr>
<tr>
<td>pH</td>
<td>4-8</td>
</tr>
<tr>
<td>Film Tackiness</td>
<td>Slight to none</td>
</tr>
<tr>
<td>Lastingness</td>
<td>&gt;3 days</td>
</tr>
</tbody>
</table>

b. Technical Specifications

This section breaks down the target properties of the 3 main components based on its function in the formulation. Because the target properties of each component depends on its compatibility with the others, Table 6 lists the general properties that are desirable for each component\(^\text{22}\). All components are ideally non-petroleum based and vegan.
Table 6. Summary of target properties of the solvent, plasticizer, and film-former.

<table>
<thead>
<tr>
<th>Component</th>
<th>Function in formula</th>
<th>Max amount in % weight of component in formulation</th>
<th>Target Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film-former</td>
<td>Binds components together when dried and thickens formulation</td>
<td>50%</td>
<td>- Forms a film at room temperature (between 68-74 degrees Fahrenheit)</td>
</tr>
<tr>
<td></td>
<td>Main component in formulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvent</td>
<td>Dissolves solutes</td>
<td>90%</td>
<td>- Low volatility (low vapor pressure)</td>
</tr>
<tr>
<td></td>
<td>Lowers the viscosity of final formulation</td>
<td></td>
<td>- Ability to dissolve film-former and plasticizer</td>
</tr>
<tr>
<td>Plasticizer</td>
<td>Increase flexibility by softening the polymer (film-former)</td>
<td>15%</td>
<td>- Molecular weight based on compatibility with film-former</td>
</tr>
</tbody>
</table>

All components should also be non-petroleum based and vegan

The film-former is the main component of the formulation, constituting up to 50% of the weight of the formulation. It binds the other components together when the nail polish dries and acts as a thickener in formulations. The American Society for Testing and Materials (ASTM) Persoz pendulum test is used to measure hardness; the value of the Persoz hardness increases with softer surfaces. For nail polish, the target range for the Persoz Hardness is between 50 and 70 oscillations. The film-former should also dry and harden at room temperature.

The solvent dissolves the other components of the formulation and lowers the viscosity of the nail polish to make it thinner and easier to apply. Solvents can make up 90% of the weight of the formulation. With the primary route of exposure to harmful solvents being inhalation, one of the target properties of a replacement solvent is low volatility. The solvent must also dissolve the film-former and plasticizer, so its chemical and physical properties such as hydrophobicity is dependent on the other components.

The plasticizer increases the flexibility of the film-former, which tends to be brittle on its own, to improve the durability of the formulation as a whole. Plasticizers can make up a maximum of 15% of the weight of the formulation. The hydrophobicity and molecular weight depends on its compatibility with the film-former, as some plasticizers can increase water permeability as well as cause phase separation.

c. **Health and Environmental Criteria**

For the hazard assessment component of the challenge, bad actor chemicals, and proposed alternatives were assessed utilizing the Green Screen Method developed by GreenScreen® for Safer Chemicals (Green Screen), a program by Clean Production Action. This comprehensive method was developed for the public to standardize hazard communication and promote the adoption of safer chemicals. The primary bad-actor chemicals were
pre-determined by the Greener Solutions teaching team, DTSC, and L’Oreal. Following the GreenScreen method, we collected hazard information sourced from Pharos, GreenScreen scores, and authoritative lists. Where information could not be obtained from authoritative lists, a toxicological literature review was conducted utilizing Google Scholar, PubMed, and Pubchem to collect data from animal studies. Dossiers sourced from the European Chemicals Agency (ECHA) were also used to examine toxicological hazards. Lastly, predictive tools (CompTox Chemicals Dashboard) were employed to collect additional information for the remaining data gaps.

Referenced authoritative lists are maintained by various countries and regions and are classified by the Global Harmonized System for Classification and Labeling (GHS) criteria. All health and environmental endpoints were reviewed, however for the occupational-centered scope of this project, we specifically discuss Group I and II health endpoints.

Utilizing the described methodology, each alternative chemical was designated a score ranging from very low to very high based on their associated toxicity. In some cases, where conflicting data was found (ie. one source scored chemical as moderate, one source as high), we designated the more conservative score to prioritize worker health. Where no data was available, the chemical was designated as having data gaps, highlighting the need for further research and testing.

The primary bad actors discussed (Tables 3 and 4) have known and potential human and environmental health hazards. Our strategies focus on improving human health endpoints most relevant to our worker demographic. The hazards of main concern for this project regard Group I and II/II* endpoints. Reference is made to fate-related endpoints regarding the sustainability of our first strategy. Below we define the health hazards discussed in our strategies (Table 7).

**Table 7.** Toxicity endpoints considered in hazard assessments (definitions sourced from Pharos).

<table>
<thead>
<tr>
<th>Group I Human Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogenicity</td>
</tr>
<tr>
<td>Ability to cause cancer or contribute to the development of cancer.</td>
</tr>
<tr>
<td>Genotoxicity/Mutagenicity</td>
</tr>
<tr>
<td>Ability to cause or increase the rate of mutations, which are changes in genetic material in cells.</td>
</tr>
<tr>
<td>Reproductive Toxicity</td>
</tr>
<tr>
<td>Ability to disrupt the male or female reproductive systems, changing sexual development, behavior, or functions, decreasing fertility or resulting in loss of the fetus during pregnancy.</td>
</tr>
<tr>
<td>Developmental Toxicity (including)</td>
</tr>
<tr>
<td>Ability to cause harm to the developing child including birth defects, low birth weight, and biological or behavioral problems that appear as</td>
</tr>
</tbody>
</table>
Neuro-developmental) the child grows.

| Endocrine Activity | Ability to interfere with hormone communication between cells, which controls metabolism, development, growth, reproduction, and behavior (the endocrine system). |

<table>
<thead>
<tr>
<th>Group II and II Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Mammalian Toxicity</td>
</tr>
<tr>
<td>Systemic Toxicity</td>
</tr>
<tr>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>Skin Sensitization</td>
</tr>
<tr>
<td>Respiratory Sensitization</td>
</tr>
<tr>
<td>Skin Irritation</td>
</tr>
<tr>
<td>Eye Irritation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistence</td>
</tr>
<tr>
<td>Bioaccumulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Hazards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flammability</td>
</tr>
<tr>
<td>Reactivity</td>
</tr>
</tbody>
</table>

d. Three-tiered Approach

We developed three strategies targeting all three key components of nail polish formulations: solvent, plasticizer, and film-former. Recognizing that each ingredient requires sufficient compatibility with all the components, we adopted a three-tiered approach to guide our
analysis. Each strategy worked through the formulation by starting with its respective component. Strategy 1 begins with a film-former replacement, then identifies a suitable plasticizer, and ultimately selects a solvent that is compatible with all the ingredients. Similarly, Strategy 2 starts with a solvent alternative before recommending film-former and plasticizer replacements. Strategy 3 focuses on identifying a plasticizer drop-in replacement and considers compatible solvents and film-formers.

**Figure 1.** Three-tiered approach.
IV. Strategy 1: Building Out a Formulation from Zein as a Film-Former

a. Inspiration: Shellac

Zein is a vegan alternative to shellac, a natural resin often used in nail polish as a film-former\textsuperscript{30}. Shellac is a purified resin secreted by lac insects or *Laccifer lacca* (also known as *Tachardia lacca*) (Figure 2)\textsuperscript{30}. These insects are usually found in trees in India and Thailand\textsuperscript{30}. Shellac comes in a variety of different colors (Figure 3) but is usually mixed with sodium hypochlorite (bleach) to remove any residual color\textsuperscript{31}. It has binding properties, gives a glossy finish, is moisturizing, and adds a shine to nail polish\textsuperscript{31}.

![Figure 2. Laccifer lacca (aka Tachardia lacca)\textsuperscript{30}.](image1)

![Figure 3. Sample shellac colors.\textsuperscript{32}](image2)

Shellac is a polymer (Figure 4)\textsuperscript{30}. The monomeric units are single esters that contain numerous hydroxyl and carboxylic acid functional groups that give it reactivity\textsuperscript{30}. Polymerization occurs via the esterification of the acid and alcohol\textsuperscript{30}.

![Figure 4. Chemical structure of shellac.](image3)

While shellac shows strong technical performance, the compound is linked to non-vegan harvesting practices and environmental degradation. During the shellac harvesting process, lac
insects are killed in the removal of large tree branches, leading to ethical concerns and non-cruelty-free and vegan preparation. Moreover, the water and energy costs associated with manufacturing shellac have often been compared to that of silk harvesting, which has been highly criticized for its environmental impact. Additionally, crop trees commonly grown on lac plantations are slow-growing and often experience stress-related tree mortality, as reported by Santanu Jha of Bidhan Chandra Krishi Viswavidyalaya in India. Increased tree mortality could lead to more planting and thus environmental degradation to maintain shellac harvest rates.

Finally, once harvested, ethanol, a volatile organic compound (VOC), is often used to liquefy shellac. VOCs have been linked to greenhouse gas emissions and large-scale habitat destruction. Various methods have been developed, however, to prepare ethanol in a bio-based manner from a range of feedstocks or using fermentation processes, minimizing overall emissions and causes for environmental concern. Overall, though, the environmental costs associated with harvesting shellac ultimately makes it a nonviable alternative to current nail polish formulations.

b. Technical and Performance Criteria

In general, the film-former should bind the components of the nail polish and thicken the overall formulation once it dries. It should also form a film at room temperature in a comparable amount of time as existing nail polish formulations.

Our first strategy focuses on developing an alternative formulation built around zein, a corn-based protein, commonly used as a vegan, shellac alternative. Like shellac, zein is a polymer but is made up of polyamides instead of polyesters (Figure 5). It is classified into four classes according to solubility: $\alpha$ (21–25 kD), $\beta$ (17–18 kD), $\gamma$ (27 kD), and $\delta$ (9–10 kD). $\alpha$-zein is the most common form (~80%) and forms a hydrophobic face looking outwards, with half of the solvent-accessible surface being occupied by hydrophobic residues.

Zein has several attributes that make it a compelling alternative to existing film-formers including its ability to form a smooth film and being a vegan, biodegradable polymer. However, similarly to nitrocellulose, zein films are brittle and require a plasticizer to increase their durability and flexibility. Zein is alcohol-soluble with a high proportion of non-polar amino acids, making it hydrophobic and difficult to dissolve in water. The films are formed
through hydrophobic hydrogen and disulfide bonds between the zein chains, and its final color depends on the type of zein polymer used and how it is processed (Figure 6). Zein can be extracted from three different corn materials: dry-milled corn (DMC), corn gluten meal (CGM), and corn distiller's dried grains with solubles (DDGS). Anderson et al. demonstrated that ground DDGS with enzyme treatment produced smooth and clear films similar to CGM control films with similar water vapor permeability. In addition to a natural yellow color from corn, zein oxidizes over time, and Zhao et al. have demonstrated the use of phenolic antioxidants to prevent this. These properties of zein act as the anchor in which we define the specifications for the solvents and plasticizers, discussed in the next section.

**Figure 6.** Zein films developed using different processes. Film A, zein extracted from CGM with 70-EtOH with 0.5% sodium bisulfite and 0.25% NaOH. Film B, made from commercial Kobayashi Zein. Film C, zein extracted from non enzyme-ground treatment DDGS with 70-EtOH; Film D, zein extracted from CGM using 88-IPA with 0.5% sodium bisulfite and 0.25% NaOH; Film E, zein extracted from enzyme-ground DDGS treatment with 70-EtOH.

### c. Specifications for Solvent and Plasticizer Alternatives

Table 8 summarizes the function, target properties, and performance criteria for the solvent and plasticizer that can potentially be paired with Zein as a film-former. In addition to its chemical compatibility with zein, chosen solvents and plasticizers must meet designated performance criteria. Solvents must be able to dissolve zein and a plasticizer, dry quickly, be shelf-stable, and have minimal to no odor. There is often a tradeoff between the performance and the toxicity of a solvent, and this strategy prioritizes finding a balance between these competing interests.

Zein is brittle on its own and a plasticizer is needed to improve its mechanical properties as a film-former. However, some plasticizers on the market increase water vapor permeability, sensitivity to moisture, and phase separation. The ideal plasticizer for this strategy must have a low molecular weight to be compatible with zein and maintain the hydrophobic properties to meet performance criteria.
Table 8. Summary of function, target properties, and performance criteria for solvents and plasticizers.

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
<th>Target Properties</th>
<th>Performance Criteria</th>
</tr>
</thead>
</table>
| **Solvent** | Dissolves components of the formulation to combine into one formulation | • hydrophobic  
• fast evaporation  
• shelf-stable  
• odorless | Ability to dissolve zein and selected plasticizer |
| **Plasticizer** | Increase the durability of the nail polish by making it flexible enough as to not crack easily once it dries | • lower molecular weight  
• less reactive to electrophilic reagents | Dissolves in selected solvent and is compatible in formulation with zein |

**d. Our Strategy**

This section outlines the methodology and justification for selecting our proposed solvent and plasticizer for the zein-based strategy (Figure 7). Due to the natural yellow and oxidizing nature, it is recommended exploring adding a blue or purple pigment to neutralize the yellow color or an antioxidant to prevent long-term discoloration due to the oxidation of the compound.

![Figure 7](image.png)

**Figure 7.** Single strategy solution based on zein as a film-former.

To guide the choice of plasticizer, a literature search was conducted to find chemicals in current nail polish formulations that are compatible with zinc. Acetyl tributyl citrate (ATBC) is a natural plasticizer used in many paints and coating in addition to 7% of nail polishes and is a good replacement for phthalates38. While zein is intrinsically rigid and brittle, studies have
shown that mixing zein with 10% tributyl citrate can achieve an ideal level of flexibility and toughness, even in high humidity and water, yielding the potential for a well-performing nail polish base with ATBC\textsuperscript{39}.

Solvent selection was driven using the GSK Solvent Selection Guide which provides concise EHS data and guidance for solvent selection (Table 9)\textsuperscript{40}. It is typically considered to be a medicinal chemistry guide for process development scientists and accordingly includes more environmental parameters than other guides\textsuperscript{41}. The caveat to many of the solvents on this list is that they have high VOC emissions, though recent development in bio-based solvents has decreased some of these issues\textsuperscript{35}. We focused on alcohols due to zein’s ability to dissolve in them and prioritized optimizing health hazards. Out of the alcohols, ethanol and isopropanol (2-propanol) are traditionally used to extract zein; zein has been shown to dissolve well in 70% ethanol\textsuperscript{42} and is commercially extracted using 88% isopropanol\textsuperscript{43}. Ethanol can also be used as the IMS–Industrial Methylated Spirits–version in which 5% methanol is added to pure ethanol to treat the solvent to be unfit for human consumption\textsuperscript{40}.

Table 9. GSK Solvent Selection Guide for alcohols.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Solvent Name</th>
<th>CAS Number</th>
<th>Composite Colour</th>
<th>Boiling Point (°C)</th>
<th>Incineration</th>
<th>Recycling</th>
<th>Treatment</th>
<th>VOC Emissions</th>
<th>Acoustic Impact</th>
<th>Air Impact</th>
<th>Health Hazard</th>
<th>Exposure potential</th>
<th>Toxicity &amp; Sensitization</th>
<th>Solubility</th>
<th>Life Cycle Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohols</td>
<td>1-Heptanol</td>
<td>111-70-6</td>
<td>Brown</td>
<td>178</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>4</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>107-21-1</td>
<td>Green</td>
<td>197</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>1-Octanol</td>
<td>111-87-5</td>
<td>Red</td>
<td>195</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>1-Butanol</td>
<td>71-36-3</td>
<td>Green</td>
<td>118</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>1-Propanol</td>
<td>71-23-8</td>
<td>Red</td>
<td>97</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>7</td>
<td>8</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Ethanol</td>
<td>64-17-5</td>
<td>Green</td>
<td>78</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>5</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>2-Propanol</td>
<td>67-63-0</td>
<td>Red</td>
<td>82</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>2-Butanol</td>
<td>75-65-0</td>
<td>Red</td>
<td>82</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>IMS (ethanol, denatured)</td>
<td>64-17-5</td>
<td>Green</td>
<td>78</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Methanol</td>
<td>67-56-1</td>
<td>Green</td>
<td>65</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

\textbf{e. Health and Environmental Criteria}

To evaluate the health and environmental endpoints associated with the proposed zein-based strategy, a hazard assessment was performed using the methodology described in our approach. After evaluating the use of zein as a film-former, we found that zein was minimally associated with toxic health endpoints (Table 10). Based on supporting authoritative lists and literature, zein had low hazard potential for allergies, immunotoxicity, cancer, development and reproductive, and skin and respiratory sensitization. Evidence suggests that zein overall poses few health hazards, with some data gaps regarding genotoxicity and endocrine activity. Though data gaps should be addressed through further toxicological testing, we are confident in moving
forward with zein given that the FDA has given zein Generally Regarded As Safe (GRAS) status when used as a direct human food ingredient. Zein was also given low product scores for concerns regarding cancer and reproductive toxicity by EWG’s Skin Deep database. Zein is biodegradable and has low environmental persistence, and bioaccumulative potential, making it an environmentally safe alternative compared to petroleum-based formulations.

**Table 10.** Hazard assessment for zein.

<table>
<thead>
<tr>
<th>Carcinogenicity</th>
<th>Genotoxicity/ Mutagenicity</th>
<th>Develop/ Reproduct Tox</th>
<th>Skin/Eye Irritation</th>
<th>Skin/Resp Sensitization</th>
<th>Endocrine Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zein</strong></td>
<td>L</td>
<td>DG</td>
<td>L</td>
<td>vL</td>
<td>DG</td>
</tr>
</tbody>
</table>

When comparing ethanol and isopropanol to secondary bad actors, ethyl and butyl acetate, they have slightly lower hazard scores regarding genotoxicity and mutagenicity (Table 11). However, because ethanol and isopropanol are volatile organic compounds (VOCs), they evaporate quickly at room temperature, which can cause high emission concentrations indoors. When inhalation, ingestion, or dermal contact with ethanol and isopropanol occurs it can cause eye, nose, and throat irritation, headaches, loss of coordination, nausea, liver damage, and adverse effects in the kidneys and central nervous system. Both ethanol and isopropanol are suspected of damaging fertility and having adverse effects on the fetus.

The International Agency for Research Cancer (IARC) categorized ethanol as a Group 1 carcinogen, meaning it is carcinogenic to humans. Notably, the designations of carcinogenicity, reproductive and developmental toxicity did not eliminate ethanol as a safe alternative in nail formulations since the high health endpoints were specifically related to ethanol in alcoholic beverages. There is currently limited data on the carcinogenicity of inhaled ethanol.

IARC categorizes isopropanol into group 3, meaning it is “not classifiable as to its carcinogenicity to humans.” In occupational exposures, where isopropanol is manufactured by the strong-acid process, there is a higher incidence of paranasal sinus cancer and an increased risk of laryngeal cancer. Isopropanol was classified as a moderate developmental and reproductive toxicant by GreenScreen. Previous reports found that absorption of isopropanol through the skin was negligible, however, some rabbit studies found that dermal absorption is possible and can cause toxicity. Although the proposed solvents are slightly safer, precautions...
need to be taken considering the remaining data gaps, particularly around potential endocrine activity.

**Table 11.** Hazard assessment for zein-compatible solvents.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Carcinogenicity</th>
<th>Genotoxicity/ Mutagenicity</th>
<th>Develop/ Reproduct Tox</th>
<th>Skin/Eye Irritation</th>
<th>Endocrine Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>L</td>
<td>L</td>
<td>M-L</td>
<td>H-L</td>
<td>DG</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>L</td>
<td>L</td>
<td>M</td>
<td>H-M</td>
<td>DG</td>
</tr>
<tr>
<td><strong>Current Solvents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butyl Acetate</td>
<td>L</td>
<td>M-L</td>
<td>M</td>
<td>H</td>
<td>DG</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>L</td>
<td>M-L</td>
<td>M</td>
<td>H</td>
<td>DG</td>
</tr>
</tbody>
</table>

**ATBC** performs well under numerous health endpoints, similar to the phthalate bad actor chemicals. ATBC was not classified by key authoritative lists and most of the toxicological studies have only investigated the health outcomes in rat studies. These studies\(^{49,50}\) provided evidence showing minimal carcinogenic, genotoxic, developmental, and reproductive effects (Table 12). Although ATBC is well studied as non-carcinogenic in rats, it has not been tested in second species. The mutagenicity of ATBC was assessed using the Ames test on several *Salmonella typhimurium* strains and was found to be not mutagenic. Moderate erythemic responses in the eye of test rabbits classified ATBC as a moderate eye irritant. Regarding skin irritation, a study tested 59 men and women and found that ATBC was non irritating to the skin, and evidence of sensitization was not observed during the study\(^{51}\).

Although not depicted in Table 12, a data gap appeared in the literature regarding respiratory sensitization since no inhalation data was available. A report\(^{50}\) prepared by the Risk Science Center at the University of Cincinnati for the U.S. Consumer Product Safety Commission suggested increased endocrine disruption caused by ATBC when studied in vitro, but concluded that the same effect was not expected to occur when studied in vivo. Moreover, Sheik and Beg\(^{52}\) highlighted the endocrine disrupting potential of ATBC using structural binding methods and suggested that the alternative plasticizer may cause dysfunction in sex steroid homeostasis. Given the remaining data gaps, we advise our partner to proceed with caution regarding this alternative.
f. Summary

In this strategy, we propose combining zein as a film-former with ethanol or isopropanol as a solvent and ATBC as a plasticizer in one iteration of a zein-based formulation. All proposed components have evidence to support that they are compatible and will dissolve well together. To improve the technical performance of this strategy, some elements to consider include incorporating different solvent mixtures (ethanol and isopropanol), antioxidants to strengthen the formula and improve shelf-life, and blue pigments or other chemicals to neutralize the yellow tones inherent to zein.

To develop other zein-based formulations, we recommend examining different solubility guides (ie. Pfizer, Sanofi) to find a wider range of potential solvents. We also recommend examining various solubility parameters (ie. Hansen, Hildebrand) if the proposed solutions are not viable. Some future considerations for this type of formulation would be utilizing other non-alcohol hydrophobic solvents to reduce toxic health endpoints and eliminate the need for an alcohol-based nail polish remover.

The film-former, plasticizer, and solvents used in this strategy overall have low hazards, but precautions need to be taken due to the data gaps they have. Since the FDA has classified zein as GRAS, we can confidently say that it is a low hazard in nail polish formulation. The plasticizer, acetyl tributyl citrate, shows low hazards among carcinogenicity, genotoxicity and developmental/reproductive toxicity with skin/eye irritation and endocrine activity being a medium hazard. It should be noted that the data used for the hazard assessment of acetyl tributyl citrate was primarily for the oral route. Inhalation data was not available. The dermal studies included irritation and sensitization data that were evaluated in both humans and animals (guinea pigs and rabbits). Sufficient animal data exists to conclude that acetyl tributyl citrate has
a medium hazard in eye/skin irritation and endocrine activity\textsuperscript{46}. The most significant concern in our proposed zein-based solution is derived from alcohol-based solvents. Yet, considering the most severe health endpoints are associated with ethanol in alcoholic beverages, we are confident that ethanol as a solvent is a safe alternative to the primary and secondary solvent bad actors.
V. Strategy 2: Water as a Solvent Alternative to Toluene

a. Water-based Formulation Overview

Our second strategy explores water as a solvent in nail polish formulations. The emissions from the nail polish can largely be attributed to the solvent, which has traditionally been toluene, with ethyl and butyl acetate as recent “safer” drop in alternatives. While these drop in replacements for toluene are relatively safe, they are still a skin and eye irritant.

Water is an appealing solvent for the clean beauty market, with no known health or environmental hazards. There are several brands offering water-based nail polish and literature exploring water as the solvent in nail polish. The literature points to some mechanical challenges to using water as a solvent, such as a long drying and curing time and its tendency to reabsorb water and become tacky again. A brief survey of customer reviews found users expressing dissatisfaction with the additional steps and precautions necessary to optimize the curing process of the nail polish. However, some of these challenges can be alleviated by additives and water remains a promising solvent in nail polish.

b. Technical and Performance Criteria

Existing water-based nail polish formulations report using unspecified acrylates copolymers as their film-former, which generally has data gaps for the health endpoints of interest. To err on the side of precaution, our team moved forward with investigating potentially safe filmers with more data that could be compatible with water as a solvent. This film-former would need to be water soluble and ideally non-petroleum based and vegan.

c. Acrylates Copolymer

Beginning with a survey of existing water-based formulations, acrylates copolymer was identified as a common plasticizer (Table 13).
Table 13. Acrylates copolymer in existing water-based formulations on the market.

<table>
<thead>
<tr>
<th>Brand</th>
<th>Film-former</th>
<th>Plasticizer</th>
<th>Full Ingredient List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquarella</td>
<td>Acrylates Copolymer</td>
<td>N/A</td>
<td>Aqua, Styrene Acrylates Copolymer, Acrylates Copolymer, Pigments</td>
</tr>
<tr>
<td>Honeybee Gardens No Nasties (peelable)</td>
<td>Acrylates Copolymer</td>
<td>N/A</td>
<td>Water (aqua), acrylates copolymer, Pigments</td>
</tr>
<tr>
<td>Sophi Piggy Paint</td>
<td>Acrylates Copolymers</td>
<td>Melia Azadirachta (Neem Oil)</td>
<td>Aqua, Acrylates Copolymers, Melia Azadirachta (Neem Oil), Pigments</td>
</tr>
<tr>
<td>Keeki Pure and Simple</td>
<td>Acrylates Copolymers</td>
<td>glycol ethers (unspecified)</td>
<td>Water, acrylate copolymer emulsion, glycol ethers, Pigments</td>
</tr>
<tr>
<td>Rosajol</td>
<td>PEG-150/Decyl Alcohol/SDMI Copolymer Polyurethane-61</td>
<td>PPG-2 Methyl Ether Polyurethane-61</td>
<td>Water, Polyurethane-61, Silica, PPG-2 Methyl Ether, Phenoxethanol, Sodium Dehydroacetate, Propylene Glycol, PEG-150/Decyl Alcohol/SDMI Copolymer, PPG-30 Butyl Ether, Ethylhexyglycerin, Bentonite, Ammonium Hydroxide, Silica Dimethyl Silylate, Tocopherol</td>
</tr>
<tr>
<td>Miniso</td>
<td>Polyurethane-1</td>
<td>propylene glycol</td>
<td>Polyurethane-1, water, propylene glycol, stearamonium bentonite</td>
</tr>
</tbody>
</table>

Of particular interest are styrene/acrylates/methacrylate copolymer plasticizers that have been developed extensively for water-based formulas\(^\text{55}\). These consist of 3 parts: styrene, ammonium methacrylate, and acrylic or methacrylic acid or the corresponding esters (Figure 8). Acrylic acid has been shown to be a respiratory toxicant, dermatotoxicant, kidney toxicant, and nervous system toxicant, and so this was eliminated from consideration\(^\text{55}\).

A popular line of this type of copolymer developed for cosmetics is the Syntran polymers from Interpolymer (now part of Zschimmer & Schwarz)\(^\text{56}\). The Syntran 5620 CG polymer in particular has been developed for nail polishes\(^\text{57}\). It lacks the methylisothiazolinone (MIT) preservative in the previous chemical Syntran PC 5620 that has been banned from cosmetics in the EU and UK and heavily regulated in the US\(^\text{58}\). Syntran PC 5620 is a white emulsion close to
physiological pH (7-8) and is not flammable at ambient temperatures, making it ideal for skin contact and shelf-stability. It has a 42% solids content, which exceeds the minimum recommendation of 40% solids for acrylates to provide ample plasticization.

From a performance standpoint, results of Syntran PC 5620 have been extensively published. For example, the overall dry time was measured for an undisclosed solvent-based formulation versus water-based formulations, one of which uses Syntran PC 5620 (Figure 9). While the solvent-based formulation dried the fastest, the water-based formulation with Syntran PC 5620 dried faster than undisclosed competitors.

![Dry Time Evaluation – ASTM D5895-03](image)

**Figure 9.** Dry time evaluation of solvent-based formulations versus water-based formulations.

The 60° specular gloss of the solvent-based and water-based formulations was also measured over time (Figure 10). The 60° specular gloss is a measure of the specular reflection of a surface, and 40 gloss units and up is typically considered high gloss. While the solvent-based formula had a consistent gloss performance over time, the water-based formulas initially started with lower gloss and had improved performance over time, likely due to the top-down drying structure. Regardless, the long-term performance of the water-based formulations were in line with the solvent-based one—the Syntran PC 5630 formula even outperformed the undisclosed solvent competitor.
Figure 10. 60° specular gloss of solvent-based formulations versus water-based formulations.

Finally, the film hardness of the solvent- and water-based formulations was measured using a Persoz hardness test (Figure 11). The oscillations measure the hardness of the surface: the amplitude of the oscillation reduces more quickly on softer surfaces than on harder surfaces. The Syntran PC 5620 water-based formula performed similarly to the solvent-based formula, even though both were softer than the competing water-based formulas.

Figure 11. Persoz hardness of solvent-based formulations versus water-based formulations.
d. Health and Environmental Criteria

Technical performance aside, acrylate copolymers have concerning health endpoints (Table 14). Styrene is a possible human carcinogen. Acute and chronic exposure to styrene results in respiratory, gastrointestinal, and neurological effects. Mice and rat studies show that acute exposure, both inhalation and oral, to styrene has low to moderate toxicity. Breathing in high amounts of styrene can further irritate the mucous membrane, eyes, and lungs. It can also affect the nervous system in similar ways to alcohol, such as by causing dizziness, tiredness, slow reaction times, balance problems, and changes in color vision. Styrene also causes problems within the male reproductive system, decreasing sperm concentration.

Dermal exposure of styrene has significant data gaps. While some studies have reported an increase of spontaneous abortions, they are inconsistent with other studies not reporting similar effects. IARC classified styrene as a group 2B carcinogen, meaning it is possibly carcinogenic to humans due to sufficient evidence of carcinogenicity in experimental animal studies. The National Fire Protection Association (NFPA) also gave styrene a serious flammability and moderate reactivity rating.

Both methacrylate ester and ammonium methacrylate copolymers have significant data gaps. Studies on guinea pigs show methacrylate ester and ammonium methacrylate copolymers are moderate sensitizers and do not have endocrine disrupting activities. Methacrylate ester was classified as a group 2B carcinogen, in which rat studies showed a positive trend of the incidence of sarcoma of the soft tissue. The incidence of malignant leukaemic tumors was increased in males exposed to methacrylate ester along with the incidence of squamous cell carcinoma of the nasal cavity. When methacrylate ester comes into contact with skin, itching, skin rash, and allergies developed. The Cosmetic Ingredient Review (CIR) expert panel determined that methacrylate ester is safe to use in nail polishes if it does not come into contact with the skin. Due to the lack of information, it was not possible to classify ammonium methacrylate copolymer as a carcinogen.

Table 14. Hazard assessment for acrylate copolymer film-former alternatives.

<table>
<thead>
<tr>
<th></th>
<th>Styrene</th>
<th>Methacrylate ester</th>
<th>Ammonium methacrylate copolymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Exposure</td>
<td>Mucous membrane &amp; Eye irritant; Gastrointestinal effects</td>
<td>Skin, eye, and nose irritant</td>
<td>Skin and eye irritant</td>
</tr>
<tr>
<td>Chronic Exposure</td>
<td>Central nervous system; Hearing loss; Peripheral neuropathy</td>
<td>Development of skin allergy; Itching; Skin rash</td>
<td>Skin and eye irritant</td>
</tr>
</tbody>
</table>
e. Natural Film-Formers

Given the health endpoints associated with acrylates copolymers, a variety of natural film-formers that dissolve in water were also explored as potential alternatives (Figure 12). Pullulan, a 100% vegetable origin natural polysaccharide. It is produced by fermentation of plant pulp and is biodegradable. While pullulan is more commonly used as an edible film in breath strips, it has also been used to successfully create peel off cosmetic masks with a drying time of 10-15 minutes and recommended 0.2-18% weight.

Alginates are another interesting class of naturally occurring, indigestible film-formers obtained from the cell walls of marine algae. Alginates contain unbranched, linear binary copolymers of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues linked by 1–4 glycosidic bonds. Alginates have been widely used in the food, beverage, textile, printing, and pharmaceutical industries in a variety of manners: as a thickener, stabilizer, emulsifier, chelating agent, encapsulator, swelling agent, suspending agent, or to form gels, films, and membranes. The charged state of alginate is particularly good for film formation. While alginic acid is water-insoluble, salts like sodium alginate have been used to prepare aqueous gel cosmetic masks.

Chitosan is another natural polysaccharide that can form films. It is derived from chitin and contains natural antibacterial properties. In fact, 8% hydroxypropyl chitosan is used in topical nail lacquer formulations to treat mild-to-moderate nail fungus and prevent microbiological attack, physical damage, and/or aggressive chemicals from reaching the nail bed. Hair products have leveraged chitosan’s cationicity which increases interaction with damaged hair fibers and skin, film-forming ability for the hair-conditioning process, and moisture retention even in low-humidity. For skin products, it has been shown to form films upon application that minimize cutaneous water loss and enhance elasticity and smoothness, in addition to serving as a moisturizing agent. The widespread use of pullulan, alginates, and chitosan in hair and skin care products make them good further directions to explore within nail polish formulations.
Figure 12. Natural plasticizer alternatives for water-based formulations.

**f. Summary**

Water-based formulations effectively eliminate bad actor chemicals used for solvents. Water is odorless and non-flammable compared to alcohols and other solvent alternatives. The performance of water-based nail polish suffers from its drying properties and potential absorption of water post-application. When applied to the nail, traditional formulations dry from the bottom of the nail polish coat outwards to the surface. However, water-based polishes dry top-down with the center drying last, leading to increased drying time and smudging. The absorption of water after the application of water based nail polishes contributes to possible inconveniences experienced by end users. For instance, the formulas can absorb water in the shower and become saturated, increasing the risk of bacterial growth on the nail. Typical solutions address these concerns by recommending 2-3 thin coats, 15 minute drying periods between coats, allowing the final result to cure for 6+ hours, and the use of antibacterial agents. Nail salons can further mitigate drying issues using fans to speed up the drying process.

While water as a solvent eliminates solvent-related hazards, it relies on compatible ingredients that may pose significant health issues. Acrylates copolymer film-formers are considered low concerns for carcinogenicity, mutagenicity, and sensitization when formed as copolymers in the final product available for end users, though significant data gaps still remain. On the other hand, acrylates in monomer form have significant health risks during their manufacturing process. In particular, the methyl and ethyl acrylate monomers are not likely to be carcinogenic to humans as defined by IARC due to inadequate evidence in human studies.
While acrylate copolymers pose low risk in the final nail polish product at known endpoints, the number of data gaps and consideration of hazardous monomers during the manufacturing process encourage exploring other recommendations. Nail salon technicians are our population of interest, but we wish to consider the occupational risk of all workers in the supply chain. Future directions should focus on investigating other possible film-formers such as the natural, water-soluble compounds discussed here: pullulan, alginates, and chitosan. How do skin and hair criteria translate to nail products?
VI. Strategy 3: Bio-based Plasticizer Drop-in Replacements

a. Technical and Performance Criteria

Plasticizers improve the durability of the nail polish by making an otherwise brittle film-forming polymer more flexible. Phthalates have been widely used in nail polish formulations for their excellent plasticizing capabilities, but are being banned or phased out due to their endocrine-disrupting properties. We aim to propose non-phthalate plasticizer drop-ins that are produced in a renewable, bio-based manner that is compatible with nitrocellulose, a commonly used film-former in conventional nail polish formulations. This plasticizer in combination with a film-former should also have a comparable hardness to existing formulations based on the Persoz pendulum hardness test. The plasticizer should also be chemically stable in formulation.

b. Industry Shifts

Industry has generally been moving away from phthalates as a plasticizer, with companies developing alternative compounds that can be used alone or combined with other plasticizers (Figure 13)\textsuperscript{72,73}. Epoxidized oils have low viscosity and high dry extract ability in addition to the potential for hypoallergenic compositions. Vernonia oils, derived from \textit{Vernonia galamensis}, have also been used as a diluent in paints\textsuperscript{74}. Sulfonamides have been shown to produce smooth film, good hardness, good resistance to wear, and gloss in nail polish formulations\textsuperscript{75}. However, sulfur-based products are associated with peeling of and irritation to the skin. Finally, cross-linked polyesters have a stable composition that produces a flexible and glossy film and have been used as plasticizers with existing film-formers like nitrocellulose\textsuperscript{76}.

![Chemical structures of epoxidized oils, sulfonamides, and cross-linked polyesters.](image-url)
c. **Natural Carbonates**

Natural carbonates have rapidly become popular alternative plasticizers in a variety of industries due to their ability to be prepared in a non-petroleum, bio-based manner\(^2\). Generic carbonates have the structure \(\text{R}_2\text{OCOOR}_2\) where:

1. \(\text{R}_1\) and \(\text{R}_2\) are equivalent; or
2. \(\text{R}_1\) and \(\text{R}_2\) form an alkyl chain with 2 or 3 carbon atoms and one or more hydroxy or hydroxy(C1-C3)alkyl groups\(^2\)

Carbonates have been shown to form a stable composition that is flexible and has a glossy film\(^2\). Diisooamyl carbonate, dilauryl carbonate and glycerol carbonate (Figure 14) have been the most widely studied\(^2\).

![Figure 14. Chemical structures of diisooamyl, dilauryl, and glycerol carbonate.](image)

De Caro et al. compared the performance of diisooamyl, dilauryl, and glycerol carbonate to acetyl tributyl citrate (ATBC) in nail polish formulation (Table 15)\(^7\) using a Persoz hardness test (Figure 15).

**Table 15.** Sample nail polish formulation using diisooamyl, dilauryl, and glycerol carbonate.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent mixture (ethyl acetate, butyl acetate, and isopropanol)</td>
<td>59.1</td>
</tr>
<tr>
<td>Film-former (nitrocellulose)</td>
<td>17.9</td>
</tr>
<tr>
<td>Polyester resin</td>
<td>13.3</td>
</tr>
</tbody>
</table>
For the Persoz hardness test, a 300μm wet film of each composition was applied to a glass plate, with measurements at regular intervals after the varnish film was dried at room temperature. The film without plasticizer did not dampen oscillations while those with plasticizer did. The results showed a moderate plasticizing effect for dilauryl and diisoamyl carbonate and a strong plasticizing effect for glycerol carbonate, even surpassing ATBC.

![Graph: Persoz hardness test of diisoamyl, dilauryl, and glycerol carbonate compared to acetyl tributyl citrate.](image)

**Figure 15.** Persoz hardness test of diisoamyl, dilauryl, and glycerol carbonate compared to acetyl tributyl citrate.

Given glycerol carbonate’s high performance, further physical and chemical properties important to nail polish were examined. Glycerol carbonate is chemically stable and non-flammable (flash point >204°C), making it shelf-stable in salons. It is also water-soluble, providing room to explore solvent-free formulations and alcohol-free removers. Its low volatility (boiling point 110–115°C at 0.1 mmHg) indicates the release of less fumes. Finally, glycerol carbonate is biodegradable and has high renewable content (76 - 100%) depending on the synthesis route, fitting our goals of a green, environmentally-friendly compound.

Regarding the synthesis of glycerol carbonate, multiple pathways have been proposed. Some of these pathways, however, are limited by toxic endpoints of starting materials, such as those with phosgene and carbon monoxide. Routes using carbon dioxide, urea, and organic carbonates are typically considered the most “green.”
The most popular bio-based formulation combines the alcohol glycerol with dimethylcarbonate (DMC). Transcarbonation from these bio-based reagents, catalyzed by $\text{K}_2\text{CO}_3$ or $\text{Na}_2\text{CO}_3$, uses mild conditions, including a less energy consuming process for glycerol carbonate separation, leading to high yields and selectivity. Changing the alcohol can produce other carbonates like diisoamyl carbonate (Figure 17) and dilauryl carbonate (Figure 18).
In solution, then, the plasticizing properties of glycerol carbonate suggest that interactions with nitrocellulose occur through hydrogen bonds between the hydroxyl functional groups of the glycerol carbonate and NO$_2$ groups of the nitrocellulose (Figure 19)$^{77}$. This arrangement generates an orderly and stable polymeric network that leads to a large and well-distributed free volume between nitrocellulose chains, resulting in high plasticization effects$^{77}$. This confirms glycerol carbonate, and the carbonates overall, are a promising class of alternative plasticizers to explore.
d. Health and Environmental Criteria

To evaluate the health and environmental endpoints associated with the proposed bio-based plasticizer drop-in replacements, a hazard assessment (Table 16) was performed using the methodology described in our approach. The three proposed carbonates were compared to acetyl tributyl citrate, the alternative plasticizer presented in Strategy 1, although this analysis will focus on the health criteria of glycerol carbonate given its superior performance over the other carbonates.

We first screened the plasticizers through authoritarian lists and found very few results. Diisomayl carbonate is featured on the Danish Environmental Protection Agency list for self-classification of hazardous substances as a moderate reproductive toxicant suspected of damaging fertility or the unborn child in QSAR modeling. As for eye irritation, glycerol carbonate is classified as causing serious eye damage under New Zealand’s Hazardous Substance and New Organism (HSNO) regulation, similar to the United Nations GHS criteria. The subsequent literature review produced very few studies on our health endpoints of interest.

Data gaps continued for endocrine activity and systemic toxicity, but our preferred plasticizer drop-in replacement, glycerol carbonate, was frequently reported by companies to ECHA with moderate levels of system toxicity of the kidneys from repeated oral exposure, and acute toxicity. Haz-Map, an occupational health database, suggested that systemic toxicity following the ingestion of glycerol carbonate is likely due to its conversion into ethylene glycol. A 1989 study experimenting on rats arrived at similar conclusions regarding glycerol carbonate’s system toxicity.

We employed predictive modeling on glycerol carbonate to address the abundance of data gaps from authoritative lists and existing literature. ToxTree is a predictive tool used to estimate toxic hazards by applying a decision tree approach. Decision trees used by ToxTree include the Cramer classification scheme used to estimate the Threshold of Toxicological Concern (TTC) for a chemical substance based on its chemical structure, and the Verhaar scheme for predicting environmental toxicity mode of actions. The application of ToxTree on glycerol carbonate resulted in the highest level of Cramer’s classification, signifying that its structure permits no strong initial impression of safety and may even suggest significant toxicity.
Table 16. Hazard assessment for carbonate plasticizer alternatives compared to acetyl tributyl citrate.

<table>
<thead>
<tr>
<th>Plasticizer:</th>
<th>Carcinogenicity/ Mutagenicity</th>
<th>Develop/ Reproductive Tox</th>
<th>Skin/Resp Sensitization</th>
<th>Skin/Eye Irritation</th>
<th>Endocrine Activity</th>
<th>Systemic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diisooamy carbonate</td>
<td>DG</td>
<td>M</td>
<td>DG</td>
<td>DG</td>
<td>DG</td>
<td>DG</td>
</tr>
<tr>
<td>2050-95-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilauryl carbonate</td>
<td>DG</td>
<td>DG</td>
<td>DG</td>
<td>VH</td>
<td>DG</td>
<td>DG</td>
</tr>
<tr>
<td>6627-63-8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycerol carbonate</td>
<td>DG</td>
<td>DG</td>
<td>VH</td>
<td>DG</td>
<td>DG</td>
<td>M</td>
</tr>
<tr>
<td>90-11-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetyl tributyl citrate</td>
<td>L-VL</td>
<td>L</td>
<td>VL</td>
<td>M-VL</td>
<td>M</td>
<td>DG</td>
</tr>
<tr>
<td>77-90-7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

None of these plasticizers are considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Data Gap | Very Low Hazard | Low Hazard | Medium Hazard | High Hazard | Very High Hazard

Sources: 29 CFR 1910.1200, Photos, Johnson, Sheldin and Bieg, 2019, EU GHS

**e. Summary**

Overall, natural carbonates show consistent yield using bio-based synthetic pathways and often outperform acetyl tributyl citrate, a leading non-phthalate plasticizer. Moving forward, we recommend optimizing technical performance by considering other glycerol esters that may have similar properties to the carbonate discussed here in addition to glycols and diols which may mimic properties of the esters. Finally, considering other non-glycerol based chemicals may also allow for more diversity in function.

Given the three carbonate plasticizer drop-in alternatives are relatively new to the industry, very little data exists on its hazardous properties associated with our health endpoints of interest. The data gaps must not be interpreted as having no hazard risk or any type of indirect approval. In fact, we suggest proceeding with extreme caution and interpreting chemicals with data gaps as possible concerns for health to account for unknown health impacts. Given the limited data available for all three carbonates and the predictive hazard analysis results from glycerol carbonate, acetyl tributyl citrate remained as our preferred plasticizer alternative.
VII. Recommendations and Future Directions

Given that we were examining whole formulation alternatives, it was not feasible to directly compare technical criteria among our strategies. Instead, the strategies have been evaluated for their potential to achieve similar results to current formulations, desired qualities, and health improvements (Table 17).

The first strategy, Building Out a Formulation from Zein as a Film-Former, provides a new and unique formulation approach that has yet to be used in commercial nail polishes. It is vegan and biodegradable, which are both qualities that appeal to our partners and the clean beauty market. Regarding performance, zein is hydrophobic and flexible, increasing the potential for a zein-based formulation to produce a flexible film that is easy to apply and has a long-lasting finish. As for health performance, zein poses few known toxic health endpoints, however, our proposed formulation will still need to be removed with an alcohol or a strong solvent so it remains a skin and eye irritant. Some of our remaining questions with Zein are regarding the use of antioxidants to prevent color change. Zein also already carries a yellow hue on its own which may not appeal to customers looking for cooler-toned hues. This issue can be addressed with blue pigment or blue chemical additives that may cancel out yellow tones.

The second strategy, Water as an Alternative Solvent to Toluene, was inspired by water-based nail polish formulations produced by L’Oreal competitors. Water is an excellent solvent that can easily be removed. Regarding performance, some issues with utilizing water as a solvent are the potential for water re-absorption and softness, as well as the potential for bacterial growth and contamination within the formula. To compensate for this, a water-based formulation requires additives to increase hardness and reduce bacterial growth. Compared to other solvents, water has a significantly slower drying time and water-based products require careful application instructions which may be a problem for some customers. Slow drying time, however, can be mitigated in nail salons with the use of fans. In concern to health performance, water has no toxic health endpoints and would vastly reduce the need for overall hazard communication and training among nail salon workers. Water-based formulations do not require strong solvents for removal, also reducing workers' exposure to formulation emissions. Moreover, there are many existing water-based formulations on the market. L’Oreal may run into some competition and patent-based issues, requiring further research. Our remaining questions regarding this strategy concern the compatibility of additives with water, and the strategy’s ability to suspend pigments.

The third strategy, Bio-based Plasticizer Drop-In Replacements, considers alternatives to phthalates that can be synthesized in a bio-based manner. This strategy provides necessary direction to our partners, considering that phthalates are soon to be phased out of cosmetics. The proposed plasticizer alternatives have significant supporting research regarding their compatibility with a variety of solvents. However, there are still many data gaps regarding their health endpoints, so moving forward with this strategy would require additional testing prior to
use. The remaining questions for this strategy regard the classification of compounds that are both plasticizers and film-formers and the percentage of the formulation weight they can make up.

**Table 17.** Strategy evaluation overview.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| 1. Building Out a Formulation from Zein as a Film-Former | ● Hydrophobic  
● Biodegradable  
● Flexible formulation  
● Strong solvent for removal | ● Requires alcohol for removal  
● Remains skin and eye irritant |
| 2. Water as an Alternative Solvent to Toluene | ● Formulation can be easily removed  
● Water = no toxic health endpoints | ● Requires additive to increase hardness + reduce bacterial growth  
● Slow dry time  
● Difficult application instructions |
| 3. Bio-based Plasticizer Drop-In Replacements | ● Synthesized in many ways  
● Compatibility between formulation components are well researched | ● Many data gaps regarding health endpoints |
VIII. Conclusions

All three strategies eliminate bad actor chemicals from the proposed formulations, which will ultimately reduce the health impacts associated with exposure to toxic chemicals in nail polish. The zein strategy presents a unique opportunity to develop a formulation that can achieve similar results to Shellac but is vegan. A water-based formulation is less likely to achieve similar results to current formulations without proper application and care. Customer reviews report dissatisfaction with drying time and application instructions, suggesting it may be a niche market to break into. Additives must also be considered to improve performance and reduce the potential for bacterial growth, which may be costly. Lastly, considering alternative plasticizers may be beneficial for the industry since phthalates are being phased out of cosmetics but will require more research and testing to be considered safer. Based on the provided evidence, we recommend moving forward with the zein strategy.
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