# Product-Chemical Profile for Nail Products Containing Triphenyl Phosphate

**JULY 2024 • DISCUSSION DRAFT**

CalEPA California Environmental Protection Agency

DTSC Department of Toxic Substances Control

SAFER CONSUMER PRODUCTS

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# 1. ABOUT THIS PROFILE

The Department of Toxic Substances Control (DTSC) identifies product-chemical combinations for consideration as Priority Products in accordance with the process identified in Article 3 of the Safer Consumer Products (SCP) regulations.[1] DTSC has determined that nail products containing triphenyl phosphate (TPhP) meet both key prioritization criteria detailed in the SCP regulations [2] for listing a Priority Product:

> (1) There must be potential public and/or aquatic, avian, or terrestrial animal or plant organism exposure to the Candidate Chemical(s) in the product; and
>
> (2) There must be the potential for one or more exposures to contribute to or cause significant or widespread adverse impacts.

This Product-Chemical Profile (Profile) demonstrates that the regulatory criteria have been met and serves as the basis for Priority Product rulemaking. The Profile does not provide a comprehensive assessment of all available literature on adverse impacts and exposure for TPhP or nail products. DTSC will finalize this Profile after considering public comments and may then start the rulemaking process. If this Priority Product regulation is adopted, the responsible entities must follow the reporting requirements pursuant to the SCP regulations.[3]

Readers should consider the following:

1. This Profile is not a regulatory document and does not impose any regulatory requirements.
2. This Profile summarizes information compiled by DTSC as of July 2024.
3. DTSC requests that interested parties provide data on the chemical and product described in this document to assist us in the evaluation process that may lead to our regulatory proposal. Written comments can be submitted using our information management system, CalSAFER,[4] prior to September 24, 2024.
4. By proposing to list this product-chemical combination as a Priority Product containing a Chemical of Concern, DTSC is not asserting that the product cannot be used safely. The proposal indicates only that there is a potential for the exposure of people or the environment to the Chemical of Concern in the Priority Product, that such exposure has the potential to cause or contribute to significant or widespread adverse impacts, and that safer alternatives should be explored.

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[1] *California Code of Regulations, title 22, Division 4.5, Chapter 55, Article 3.*
[2] *California Code of Regulations. title 22, section 69503.2(a).*
[3] *California Code of Regulations title 22, section 69503.7 and Article 5 (Alternatives Analysis)*
[4] *https://dtsc.ca.gov/scp/nail-products-containing-tphp/*

**Candidate Chemical:** A chemical that exhibits a hazard trait and is listed on one or more authoritative lists in the SCP regulations.

**Product-Chemical Profile:** A report generated by DTSC to explain its determination that a proposed Priority Product meets the SCP regulatory criteria for potential significant or widespread adverse impacts to humans or the environment.

**Priority Product:** A product-chemical combination as identified in regulation by DTSC that has the potential to contribute to significant or widespread adverse impacts to humans or the environment.

## 2. EXECUTIVE SUMMARY

DTSC proposes to list nail products containing triphenyl phosphate (TPhP) – including nail coatings, nail art, and nail and cuticle treatments – as a Priority Product.

Many nail coatings and treatments intentionally contain TPhP as a plasticizer, which makes the products more flexible and increases their durability. TPhP may also be present as a contaminant. Exposure to TPhP from nail products has the potential to cause or contribute to adverse human health impacts.

The primary route for exposure to TPhP from nail products is through dermal contact, with inhalation potentially contributing as well. TPhP has been shown to be readily absorbed into the body through the skin based upon the appearance of the metabolite diphenyl phosphate (DPhP) in urine. Incidental ingestion of TPhP found in dust is also possible, but is not a key exposure route for nail products. Exposure to TPhP exhibits liver toxicity in experimental animal studies, resulting in changes to body weight and metabolic activity. There is suggestive evidence that TPhP exhibits endocrine, developmental, neurodevelopmental, and reproductive toxicity.

TPhP is efficiently metabolized in the skin and body to DPhP, the main urinary metabolite of TPhP. Application of nail products containing TPhP significantly increases DPhP urine levels over a 24- to 48-hour period. Further, there is some evidence that nail salon workers' post-shift urinary DPhP levels are higher than pre-shift levels. Studies of nail salon workers demonstrate that, on average, they have higher urinary DPhP levels than the general population.

Use of nail products has the potential to expose nail salon workers, patrons, and nail product consumers to TPhP. TPhP has been detected in indoor air in nail salons in California, and nail salon workers have an especially high potential for exposure. The magnitude of TPhP exposure can be affected by several factors:

- **Ventilation:** Nail salons often have inadequate ventilation.
- **Length of work shift:** Salon workers often work more than eight hours per day and 40 hours per week.
- **Access to information**: Salon workers often face barriers to accessing adequate information on chemical safety. Safety Data Sheets, if available, may be challenging for workers to comprehend, particularly if English is not their native language.
- **Use of personal protective equipment**: Salon workers are often not provided with proper personal protective equipment such as nitrile gloves and respirators that can reduce exposure to TPhP.
- **Other factors:** Building size, room dimensions, etc. can affect indoor air exchange rates, which in turn influence the degree of TPhP exposure in nail salons and at home.

In California, most nail salon workers are Vietnamese immigrants of lower socioeconomic status and are often women of childbearing age. As a group, they are more likely to experience occupational exposures to TPhP than the population at large and, as such, represent a disproportionately impacted community. In addition to being exposed to chemicals on the job, nail salon workers may also experience other environmental and socioeconomic stressors that can act cumulatively to affect their health, contributing to persistent environmental health disparities.

Fetuses, infants, and children are especially vulnerable to the harmful effects of exposure to TPhP. Nail salon workers who work while pregnant risk exposing their fetuses to TPhP in the womb. TPhP has been detected in breast milk, and nursing mothers who work in nail salons can expose their infants when they breastfeed. Salon workers who bring their infants and children to work may expose them to TPhP vapors present in indoor air.

Nail products and professional manicure/pedicure services are popular in the United States (U.S.). In California alone, there are 7,897 nail salons and approximately 130,000 licensed manicurists. Nail products, including products containing TPhP are also widely used at home. Retail sales of nail products exceeded $1.3 billion in the U.S. in 2019, with nail polish sales representing more than 33% of this amount.

In 2020, DTSC requested information on various nail products from product manufacturers, importers, assemblers, retailers, distributors, and trade associations. TPhP was reported in 1,154 nail products; it was identified both as an added ingredient, with concentrations ranging from 0.1 to 10%, and as a contaminant, with concentrations ranging from 0 to 0.1%. (It is unclear whether the reported concentration ranges are represented in weight/weight (w/w) or weight/volume (w/v).) The reported products included solvent-based nail coatings, primers, bonders, UV gel polish, hardeners, and other nail products. Several years ago, DTSC's Environmental Chemistry Laboratory tested 156 retail and professional-use nail products and detected TPhP in 17 nail products at concentrations ranging from 8,880 ppm to 46,100 ppm (µg/mL) (0.88 to 4.61% w/v).

The U.S. Food and Drug Administration (FDA) is the federal agency with regulatory oversight responsibility over nail products and other cosmetics. However, the FDA's authority to regulate chemicals in nail products is limited. The agency lacks authority to require safety testing of nail products, and there is no approval process for nail products prior to sale in the U.S. Moreover, there is no legal requirement to report adverse impacts related to nail products, and the FDA has no recall authority over such products.

Based on the factors discussed above, DTSC has determined that exposure to TPhP-containing nail products may contribute to or cause significant or widespread adverse impacts to nail salon workers, women, infants, children, and disproportionately impacted communities and proposes to identify nail products containing TPhP as a Priority Product.

The SCP Regulations[5] require that DTSC set an Alternatives Analysis Threshold (AAT) if the Chemical of Concern in a Priority Product is present as a contaminant.[6] Because TPhP can be present as a contaminant in nail products, DTSC plans to specify an AAT for TPhP in nail products. Manufacturers of Priority Products with TPhP concentrations below the AAT value can choose to submit an Alternatives Analysis Threshold Notification in lieu of conducting an Alternatives Analysis or other means of complying with the Safer Consumer Products Regulations. As of this writing, DTSC plans to set the AAT at 250 ppm in its proposed regulations to list nail products with TPhP as a priority product.

## 3. PRODUCT DEFINITION AND SCOPE

*This section describes the product that forms the basis for the proposed product-chemical combination.*

DTSC is proposing to list Nail Products containing TPhP, as either an added ingredient or contaminant, as a Priority Product. The definition of nail products, as used by SCP, encompasses a variety of products such as nail coatings, nail art, and nail cuticle treatments.

"Nail coatings" refers to any clear or colored paint, polish, lacquer, enamel, or gel product marketed or sold for application to the fingernails or toenails. There are three types of nail coatings: solvent-based nail coatings, ultraviolet (UV) gel nail coatings, and nail art paint.

- "Solvent-based nail coatings" are clear or colored nail coatings that form a hard coating on nails upon evaporation of their solvents. These products do not require UV light to cure. Subproducts include nail polishes, lacquers, enamels, water-based polishes, base coats, undercoats, top coats, nail hardeners, gel nail polishes, and gel-like polishes.

[5] *California Code of Regulations, title 22, section 69503.5(c)*

[6] *A contaminant is defined as a chemical that is unintentionally present that does not contribute to the function or performance of the product. An ingredient is a chemical that is intentionally added to a product and contributes to the overall function and performance of the product.*

    - "Nail polish" is a varnish or paint applied to the fingernails or toenails to color them or make them shiny.
    - "Lacquer" or "enamel" is a coating that dries by means of solvent evaporation.
    - "Base coat" or "undercoat" is a clear or milky-colored coating that is used before applying other coatings to the nail. It may be marketed for strengthening or protecting the nail, restoring moisture to the nail, or helping other coatings to adhere to the nail.
    - "Top coat" is a clear coating that is used after applying other coatings to the nail. It may be used to protect underlying coatings or to add shine, gloss, or matte to the nail.
    - "Strengthener" or "hardener" is a coating that is applied to the nail that is marketed to help with cracking, splitting, peeling, or breaking of the fingernails or toenails.
    - "Gel nail polish" or "gel polish" is a gel varnish coating with a look and feel similar to UV gel but that may not require a UV or LED (light-emitting diode) lamp to dry. Gel polish typically contains color but can also be a clear nail coating.
    - "Ridge Filler" is a coating that is applied to the nail to prepare the nail surface for smoother application of other coatings to the nail.
- "UV gel nail coatings" are clear or colored gel nail coatings that are cured or hardened on nails using a UV or a LED lamp rather than solvent evaporation. Subproducts include UV gel nail polish, UV gel top coat, UV gel base coat, hard gel, and Shellac.
    - "Gel," "UV gel," "gel effect nails," or "nail gel" is a pre-mixed coating that is hardened using a UV or LED lamp.
    - "Shellac" is the brand name for a nail product created by Creative Nail Design. It is a hybrid coating that is a combination of nail polish and gel. Shellac is applied directly onto natural nails and cured using UV light.
    - "Hard gel" is a pre-mixed coating with high solvent resistance; it is hardened using a UV or LED lamp. It can be applied directly onto natural nails to provide additional strength or can be sculptured using nail enhancements.
- "Nail art paint," refers to any decorative paint, including solvent-based or UV gel nail coating overlays of nail polish, UV gel, airbrush paints to nails, or hybrid coatings like Shellac. "Airbursh nail art paint" is a subproduct of "nail art paint".
    - "Airbrush nail art paint" means a nail art paint that is designed or intended to be sprayed onto the nail by a device using compressed air. This product may also be labeled "ink," "polish," "paint," or "pigment for airbrush nail art."

"Nail or cuticle treatment" is any product that is designed to treat the nail or cuticle region of the nails. This includes cosmetic treatments designed to care for the nail, such as to soften and remove overgrown cuticles and dead skin. The treatment may also provide health benefits or nutritional

benefits to the fingernail region or toenail region. Nail treatments may also be nail coatings designed to prepare the nail surface for additional cosmetic application.

Nail coatings, nail art, and nail treatments include, but are not limited to, products that can be categorized by Global Product Classification (GPC) identified by the following codes (GS1 2021):

- Segment: 53000000 – Beauty/Personal Care/Hygiene
    - Family: 53160000 – Cosmetics/Fragrances
        - Class: 53161200 – Nail Cosmetic/Care Products
            - Brick: 10000360 – Cosmetics – Nails (nail coatings)
            - Brick: 10000361 – Nails – Treatments
            - Brick: 10000385 – Nails – Accessories (Non Powered)
            - Brick: 10000778 – Nail Cosmetic/Care Products Other
            - Brick: 10000359 – Nails – False
                - Attribute: 20000292 – Type of False Nails
                    - Value: 30004466 – FALSE NAILS UV GEL
                - Attribute: 20000794 – Type of Material
                    - Value: 30004342 – UV ACTIVATED GEL

## 3.1. Alternatives Analysis Threshold Definition

The Alternatives Analysis Threshold (AAT) is the minimum concentration of a Chemical of Concern in a Priority Product below which a manufacturer is exempt from performing an Alternatives Analysis (AA).[7] DTSC may set an AAT for a Chemical of Concern that is an intentionally added ingredient and must do so if the Chemical of Concern is a contaminant. DTSC may also specify an AAT concentration greater than the applicable Practical Quantitation Limit (PQL)[8] for any Chemical of Concern that is a contaminant. DTSC proposes an AAT of 250 ppm for TPhP in nail products. The justification for this proposal is provided in Appendix C.

[7] *California Code of Regulations, title 22, section 69505.3*

[8] *The PQL is defined as "the lowest concentration of a chemical that can be reliably measured within specified limits of precision and accuracy using routine laboratory operating procedures" (California Code of Regulations, title 22, section 69501.1(a)(52).)*

# 4. CANDIDATE CHEMICAL DEFINITION AND PROPERTIES

*This section introduces the Candidate Chemical in the proposed product-chemical combination.*

Triphenyl phosphate (TPhP) (CAS No. 115-86-6) is a non-halogenated aromatic[9] phosphate ester and is listed as a Candidate Chemical (CC) on DTSC's Candidate Chemicals List (CC List) based on its identification as a Priority Chemical under the California Environmental Contaminant Biomonitoring Program (Biomonitoring California) (Biomonitoring California 2019; DTSC 2019) (Figure 1). TPhP functions as a plasticizer in nail products, primarily in nail coatings and nail treatments (Mendelsohn et al. 2016), and provides durability and flexibility. TPhP may also be present as a contaminant in nail products (DTSC 2023a). TPhP is also used in a variety of products as a plasticizer and flame retardant (Mendelsohn et al. 2016; Biomonitoring California 2019). Industrially, TPhP is produced by a reaction between phosphoric acid and phenol (NIH 2021a).

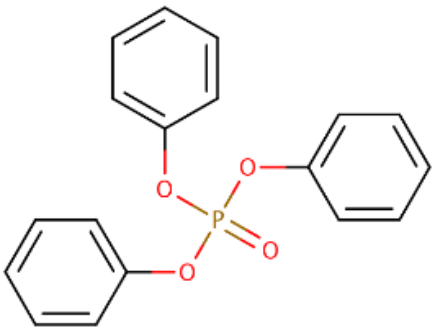


*Figure 1. Chemical structure of triphenyl phosphate (TPhP) (NIH 2021a).*

Triphenyl phosphate is commonly abbreviated as TPhP; however, sometimes the abbreviation TPP is used. The TPP abbreviation is problematic because there are at least two other chemicals – triphenyl phosphite and tripropyl phosphate – that may use the same abbreviation.

Common synonyms and trade names of TPhP (listed by NIH (2021a), unless otherwise referenced), include:

- Phosphoric acid triphenyl ester
- Celluflex TPP;
- Disflamoll TP;
- Phenyl phosphate ($(PhO)_3PO$);

[9] *Halogens are chemical elements that share chemical properties and characteristics. Examples include fluorine, chlorine, and bromine. Non-halogenated chemicals do not contain any halogen elements. A chemical is considered aromatic when it contains flat, ring-like portions that tend to be stable (in other words resist structural change).*

- Phosflex TPP;
- Reofos TPP;
- Trifenylfosfat [Czech];
- Sumilizer TPP (U.S. EPA 2020a);
- Wako TPP (U.S. EPA 2020a);
- EVERFOS TP (ECHA 2020);
- Pilabrac 521® (UK Environment Agency 2009); and
- Reomol TPP® (UK Environment Agency 2009).

## 4.1. Relevant physicochemical properties

*Reference: California Code of Regulations, title 22, section 69503.3(a)(1)(D).*

*Physicochemical properties can be helpful in predicting a chemical's behavior. A chemical's behavior in humans, wildlife, ecosystems, and the environment may indicate potential adverse public health and environmental impacts.*

Relevant physicochemical properties are listed in Table 1, below. TPhP appears as colorless crystals at room temperature, and although TPhP is not soluble in water, it can readily dissolve in many oils and solvents such as acetone, and lacquers (NIH 2021a).

*Table 1. Physicochemical Properties of TPhP.*

| Property | Values | References |
|---|---|---|
| Physical state | Solid | (NIH 2021a) |
| Molecular weight | 326.288 g/mol | (U.S. EPA 2020a) |
| Density | 1.25 g/cm$^3$ (predicted average) | (U.S. EPA 2020a) |
| Vapor pressure | 0.001 Pa | (ECHA 2024a) |
| Water solubility (WS) | 1.9 – 2.1 mg/L | (ECHA 2024a) |
| Log octanol-water partition coefficient (Log $K_{ow}$) | 4.63 | (ECHA 2024a) |
| Log octanol-air partition coefficient (Log $K_{oa}$) | 10.8 (predicted average) | (U.S. EPA 2020a) |
| Log soil adsorption coefficient (Log $K_{oc}$) | 4.07 (predicted average) | (U.S. EPA 2020a) |
| Henry's Law Constant (H) | 1.86 x $10^{-6}$ atm-m$^3$/mol (predicted average) | (U.S. EPA 2020a) |

Based on its log $K_{ow}$[10] value of 4.63 (Table 1), TPhP has a potential for bioaccumulation, as the SCP Regulations set a threshold log $K_{ow}$ value greater than or equal to 4.0 as evidence that a chemical has bioaccumulation properties (22 CCR 69405.2). The log $K_{oa}$[11] value of 10.8 provides further support that TPhP has bioaccumulation potential, as the SCP Regulations set a threshold log $K_{oa}$ value greater than or equal to 5.0 as evidence of bioaccumulation properties (22 CCR 69405.2).

Further, TPhP is expected to be slightly volatile based on its Henry's law constant of 1.86 x $10^{-6}$ atm-$m^3$/mol. Chemicals with Henry's law constants that are between 3 x $10^{-7}$ and 1 x $10^{-5}$ atm-$m^3$/mol are expected to have some tendency to escape from water to air (Minnesota DH 2015).

The European Commission (EC) defines volatile chemicals as those whose vapor pressure is equal to or greater than 10 Pascal (Pa) at 20 °C (EC 1999). Based on this definition, TPhP, with a vapor pressure of 0.001 Pa (Table 1), would be considered nonvolatile. Nevertheless, based on its Henry's law constant, some volatilization of TPhP is expected to occur at standard temperature and pressure (STP).

## 4.2. Environmental fate

*Reference: California Code of Regulations, title 22, section 69503.3(a)(1)(E).*

*Environmental fate describes a chemical's mobility in environmental media, transformation (physical, chemical, or biological), or accumulation in the environment or biota. A chemical's environmental fate in air, water, soil, and living organisms relates to its exposure potential hazard traits, as defined in the California Code of Regulations, Title 22, Chapter 54.*

As a class, phosphate esters such as TPhP have relatively low water solubility (1.9 mg/L at 25 °C), low vapor pressure, high $K_{ow}$, and high $K_{oc}$.[12] TPhP is well documented to have a greater affinity for soil and sediment over water (log $K_{oc}$ value of 4.07, Table 1), and consequently, TPhP is primarily found in soil or sediment in the environment and is unlikely to migrate to groundwater (ATSDR 2012). In addition, TPhP that is bound by soil or sediment is unlikely to leach into water (ECHA 2020). A fugacity model[13] predicts that the majority of TPhP that is released equally to air, water, and soil will be found in the soil (94.2%) at steady state conditions (UK Environment Agency 2009). TPhP released to only water is predicted to be found in water and sediment at similar percentages (UK Environment Agency 2009).

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[10] *$K_{ow}$ values measure a chemical's ability to partition from an aqueous phase (water) to an organic phase (octanol) and are displayed as the log of $K_{ow}$. Chemicals with high log $K_{ow}$ values have a higher preference for the organic phase than for the aqueous phase, and easily partition into octanol.*

[11] *$K_{oa}$ values measure a chemical's ability to partition from an organic phase (octanol) to a gaseous phase. Chemicals with high $K_{oa}$ values have a higher preference for the organic phase.*

[12] *$K_{oc}$ values measure the ability of a chemical to adsorb onto soil or sediment rather than remain in the aqueous phase and are displayed as the log of $K_{oc}$.*

[13] *A fugacity model is a tool for predicting the fate of a chemical in the environment.*

As discussed in Section 4.1, some volatilization of TPhP is expected. In the atmosphere, TPhP is anticipated to undergo phototransformation via reactions with hydroxyl radicals, with an estimated half-life of 12 to 36 hours (UK Environment Agency 2009; ANSES 2019). Although these half-lives are relatively short, TPhP has been measured in air, water, snow, and sediment in the Arctic, which may result from both local sources and long-range transport in air and water (Li et al. 2017; Sühring et al. 2021). When bound to atmospheric particles, organophosphate esters such as TPhP can persist in the atmosphere for days to weeks, despite phototransformation (Liu et al. 2014). A number of factors, including relative humidity, chemical composition of the particle, and phase may increase atmospheric transport of these compounds (Yu et al. 2016; Liu et al. 2019).

TPhP is not classified as environmentally persistent, based on evidence indicating a short half-life of less than 40 days in freshwaters[14] (ECHA 2020), rapid hydrolysis in alkaline waters (pH > 7) (ATSDR 2012), and rapid biodegradation of less than 10 days in aquatic environments, sewage, and sludge (ATSDR 2012; ECHA 2020). Data summarized by the European Chemicals Agency (ECHA) and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) indicates that TPhP has low to moderate bioaccumulation potential in aquatic organisms due to its log $K_{ow}$ value of 4.59 (ANSES 2019; ECHA 2020). As previously discussed, TPhP meets the criteria for bioaccumulation in 22 CCR 69405.2 (log $K_{ow}$ value greater than or equal to 4.0). Results from trophic studies indicate a low trophic magnification potential; therefore, it is unlikely that TPhP undergoes biomagnification (Brandsma et al. 2015; Hallanger et al. 2015; Greaves et al. 2016; Zhao et al. 2018; Wang et al. 2019d; Ding et al. 2020).

## 4.3. Absorption, Distribution, Metabolism, and Excretion

*Reference: California Code of Regulations, title 22 section 69407 (additional relevant information)*

*This section summarizes relevant data on the relationship between exposure to a given chemical substance and degree of response. Absorption, distribution, metabolism, and excretion information from well-conducted studies can be helpful in describing or quantifying the relationship between exposure concentration or dose and degree of adverse effect or biological response.*

### 4.3.1. Absorption

TPhP is absorbed into the human body through various exposure routes. Dermal absorption is considered a primary exposure pathway for TPhP in consumer products that come in contact with human skin (Mendelsohn et al. 2016), such as flame retardants and plasticizers (U.S. EPA 2020b). Inhalation can also be a significant route, especially in occupational settings where TPhP in suspended

[14] *Title 22, section 69405.3, division 4.5, chapter 54 of the California Code of Regulations (CCR) states a chemical substance is environmentally persistent if the half-life in fresh water is greater than 40 to 60 days (22 CCR 69405.3).*

dust is inhaled (Estill et al. 2019). Oral absorption can also occur and may be an important route of exposure for TPhP present in indoor dust (Xu et al. 2019).

Once absorbed, TPhP can be distributed throughout the body via the bloodstream, reaching various tissues and resulting in systemic exposure before metabolism and elimination (Chen et al. 2020). TPhP's primary urinary metabolite, DPhP, has been used as an indicator of TPhP exposure and absorption (Wang et al. 2021a). (Further discussion of TPhP metabolism is below in Section 4.3.3). Observational human biomonitoring studies examining the association of TPhP levels in environmental media (products, air, surface dust, floor dust, hand wipes, food) with internal measures of exposure (typically DPhP in urine) have usually reported weak or no correlations with any individual media (Meeker et al. 2013; Hoffman et al. 2014; Dodson et al. 2014; Hammel et al. 2016; Butt et al. 2016; Castorina et al. 2017a; Larsson et al. 2018; Phillips et al. 2018; Gibson et al. 2019; Xu et al. 2019). This may be due to the multiple sources of exposure and the difference in individual behaviors (associated with age, gender, race, socioeconomics) that need to be controlled for (Ospina et al. 2018), as well as other confounding sources of DPhP in urine besides TPhP (Yang et al. 2020; Liu et al. 2021b). Therefore, the primary evidence of absorption by each route of exposure comes from controlled experiments in humans or animals.

#### *4.3.1.1. Dermal*

Studies in humans, animals, and *in vitro* have found evidence of absorption of TPhP through the skin. Mendelsohn et al. (2016) found elevated levels of DPhP in urine after application of nail polish containing 0.97% TPhP. Sixteen participants showed a geometric mean[15] increase of 6.59-fold over background levels 10-14 hours post-application, indicating the absorption of TPhP. In a subsequent study with 10 participants, DPhP levels in urine remained elevated 24 hours after application of nail polish (Mendelsohn et al. 2016). In contrast, participants who wore gloves with artificial nails attached showed no increases in DPhP concentrations in the urine after application of nail polish on the artificial nails. This indicates that dermal absorption of TPhP is the main pathway of exposure. Mendelsohn et al. (2016) estimated that 0.1 to 2.2% of TPhP is absorbed when applied to the nail. In another study, nail polish containing 4% TPhP was applied to four participants, and increased levels of DPhP in urine were observed over a 24-hour monitoring period (Grau et al. 2019). This study also reported the detection of unmetabolized TPhP in the urine of volunteers one to two hours after nail polish application at levels below the quantitation limit of 6.7 ng/L. A study that estimated skin penetration rates for several organophosphate chemicals using human abdominal skin from three donors found that TPhP dissolved in a solution of ethanol and toluene showed very slow and limited absorption up to 72-hours after exposure and accumulation in the epidermal layer of the skin (Frederiksen et al. 2018). A second study using a reconstructed skin model (EPISKIN™) that measured TPhP over a 24-hr period

[15] *A type of average that is less influenced by a small number of higher concentration values.*

made the same observations (Zhang et al. 2022), with the estimated absorption rates only varying by a factor of 2.3 from the study that used human skin (Frederiksen et al. 2018).

These studies provided insight into TPhP dermal absorption dynamics. In summary, the primary route of exposure to TPhP in nail products is dermal. There are other factors that affect dermal absorption, such as variability in metabolic enzymes, thickness of the skin at the site of dermal contact, and the ability of TPhP to inhibit the metabolic enzymes (Abdallah et al. 2019). Additionally, the metabolism of TPhP to DPhP in the skin may play a significant role in limiting the systemic absorption of TPhP throughout the body (see Section 4.3.3).

#### *4.3.1.2. Inhalation*

A study in mice assessed the uptake of a mixture of organophosphate flame retardant chemicals, including TPhP, delivered to the respiratory tract by intratracheal instillation (through a tube inserted into the trachea) (Chen et al. 2020). The mice were dosed once daily for three days at a range of concentrations corresponding to 0.36, 3.6, and 36 µg/day. TPhP was found in 10 different tissues at significantly increased concentrations in the two highest-dose groups compared to controls, suggesting inhalation as a route of exposure. Additionally, DPhP was detected in urine (Chen et al. 2020), but it was not quantified in this study.

#### *4.3.1.3. Oral*

Several studies have administered TPhP, its metabolite DPhP, or TPhP-containing mixtures to experimental animals orally and subsequently measured TPhP or DPhP in their bodies or urine (Phillips et al. 2016; Baldwin et al. 2017; Krumm et al. 2018; Liu et al. 2020; Selmi-Ruby et al. 2020; Ma et al. 2021; Witchey et al. 2022). Limited absorption of TPhP was generally observed in mice orally dosed with TPhP either through oral gavage or dissolved in drinking water (Selmi-Ruby et al. 2020). The following key studies summarize the absorption of TPhP after oral exposure.

One experiment measured the blood levels of TPhP and DPhP after dosing mice via gavage with 0.1, 1, 10, or 100 µg of TPhP (Selmi-Ruby et al. 2020). After one hour, TPhP was detected in only one out of five animals in the highest-dose group of 100 µg. Blood concentrations of the metabolite DPhP were significantly elevated only in the 10 and 100 µg dose groups (Selmi-Ruby et al. 2020), indicating an approximately two-fold increase in DPhP levels with increasing TPhP doses. The study also orally dosed mice with DPhP but in much lower concentrations (0.1 and 1µg) (Selmi-Ruby et al. 2020). A proportional dose-dependent increase in DPhP levels in blood was observed between dose groups (i.e., a 10X higher dose resulted in an approximately 10X higher level of DPhP in blood). These significant increases in DPhP in blood were observed using doses that were 100 times lower than the doses used in the TPhP experiment, highlighting a significant disparity in relative bioavailability between TPhP and DPhP, with DPhP exhibiting considerably higher absorption rates. The low relative bioavailability of TPhP to DPhP indicates that only a small percentage of TPhP was absorbed.

In the second experiment, mice were given 0.1, 1, and 10 mg/L of DPhP or TPhP (estimated intake of approximately 0.5, 5, or 50 µg) in drinking water overnight (when the mice are most active). For mice given DPhP, blood and liver analysis indicated a dose-dependent increase in DPhP in these tissues (Selmi-Ruby et al. 2020). However, for mice given TPhP in drinking water, TPhP was not detected and DPhP was not significantly elevated in the blood or the liver. These experiments again indicate that TPhP was poorly absorbed in mice following oral exposure.

In a study by Ma et al (2021), mice were dosed with 50 mg/kg body weight of TPhP by oral gavage, and the levels of TPhP in blood serum were examined over a 24-hr period. Blood serum levels of TPhP in mice peaked two hours after exposure and were similar to background levels after 24 hours (Ma et al. 2021). This study demonstrates that following higher oral exposure to TPhP, there is some absorption of TPhP in mice.

In another study, pregnant and nursing rats were dosed orally in food with 1 and 3.3 mg/kg-day of Firemaster 550®, which contains approximately 18% TPhP (Phillips et al. 2016). At the end of the dosing period, serum collected from the mothers showed that TPhP levels were below the detection limit. However, DPhP was measurable in the urine of the mothers in both the low- and high-dose groups, indicating TPhP uptake in rats (Phillips et al. 2016).

### 4.3.2. Distribution

Studies in mice indicate that following absorption into the body, TPhP can be detected in blood (Ma et al. 2021) and distributed across ten different tissues throughout the body (Chen et al. 2020). Tissue accumulation of TPhP was not associated with lipid content despite the chemical's lipophilic nature (Chen et al. 2020).

In multiple human biomonitoring studies, TPhP or DPhP have been detected in whole blood, plasma, and serum (Zhao et al. 2017; Zhao et al. 2019; Xu et al. 2019; Ya et al. 2019; Gao et al. 2020; Wang et al. 2020b; Hou et al. 2020). The additional TPhP metabolites 4-hydroxyphenyl diphenyl phosphate (4-HO-TPhP) and 3-hydroxyphenyl diphenyl phosphate (3-HO-TPhP) identified by Van den Eede et al. (Van den Eede et al. 2013; Van den Eede et al. 2016a) (see Section 4.3.3) were not detected in whole blood or serum in two studies (Zhao et al. 2019; Xu et al. 2019). A study performed to investigate the kinetics of organophosphate ester clearance from the body reported that the majority of the TPhP partitioned into plasma (63%) and also showed that TPhP has a high affinity for plasma proteins, such that less than 5% of the TPhP in blood is expected to be free (unbound) (Wang et al. 2020b). One human biomonitoring study that measured TPhP in both plasma and blood cells also reported that TPhP preferentially partitions into plasma (Zhang et al. 2023). Because TPhP is widely distributed in the body and binds to proteins, reduced rates of TPhP clearance from the body can be expected. TPhP can also pass into the central nervous system. In a study of 288 patients at a hospital in China, the median ratio of TPhP in cerebral spinal fluid to blood serum was 1.07, highlighting the potential for TPhP to access

the central nervous system (Hou et al. 2022). Similarly, studies in mice and rats have also reported increased concentrations of TPhP in the brain following TPhP exposure (Chen et al. 2020; Liu et al. 2020; Witchey et al. 2022).

TPhP has also been measured in human placenta (Ding et al. 2016), human cord blood (Wang et al. 2021b), and in tissue composed of human embryo and the surrounding chorionic villi[16] (Zhao et al. 2017), indicating the potential for exposure prior to birth resulting from maternal exposure. Zhao et al. (2017) hypothesized that the high affinity of TPhP for the thyroid hormone transport protein transthyretin may mediate the transfer to the human embryo. In rats orally dosed with high amounts of TPhP during pregnancy, TPhP was detected in amniotic fluid, placenta, and fetuses (Witchey et al. 2022). Lower dose oral exposure studies of rats detected TPhP in the placenta but not the fetuses (Phillips et al. 2016; Baldwin et al. 2017). Additional information about transplacental transfer can be found in Section 4.4.2.1.

TPhP has been detected in human breast milk in multiple studies (Sundkvist et al. 2010; Kim et al. 2014; Ma et al. 2019), indicating the potential for lactational transfer to offspring. Evidence of lactational transfer was observed from measured TPhP at the time of weaning in rat pups whose mothers were dosed in feed from gestation through weaning (Witchey et al. 2022). Further details about lactational transfer can be found in Section 4.4.2.1.

### 4.3.3. Metabolism and biotransformation

The metabolism of TPhP in humans is not fully understood. However, studies indicate that humans can metabolize TPhP into a number of products. Information on TPhP metabolism presented in this section comes from studies using whole cells or cell extracts from different human and animal tissues.

In human liver cells, TPhP undergoes Phase I metabolism[17] by cytochrome P450 (CYP) monooxygenase enzymes to form multiple metabolites (Figure 2) including mono and dihydroxylated[18] metabolites of TPhP and DPhP (Van den Eede et al. 2013; Van den Eede et al. 2016a; Zhang et al. 2018). CYP1A2 and CYP2E1 are the primary CYP isoforms responsible for TPhP metabolism in liver cells (Zhang et al. 2018). While CYP enzymes are responsible for most of the metabolism of TPhP to DPhP, the activity of

*[16] Chorionic villi are threadlike projections from the surface of the outermost membrane (chorion) of the embryo that increase the surface area by which maternal blood is made available to the fetus.*
*[17] Phase I metabolism refers to small changes made to molecules by different metabolic enzymes, including addition of oxygen atoms or cleavage of molecules to reveal more polar functional groups, which make molecules more water soluble and easy to eliminate from the body.*
*[18] A hydroxyl group is an oxygen atom and a hydrogen atom, denotated as HO in the name of individual chemicals.*

unspecified esterases[19] in liver cells can also contribute to DPhP generation (Zhang et al. 2018). DPhP is estimated to make up 20-48% of the liver metabolites (Van den Eede et al. 2013; Zhang et al. 2018; Phillips et al. 2020).

The main hydroxylated metabolite observed in human liver cells is 4-hydroxyphenyl diphenyl phosphate (4-HO-TPhP), along with a hydroxylated diphenyl phosphate that is likely 4-hydroxyphenyl phenyl phosphate (4-HO-DPhP) (Van den Eede et al. 2013; Van den Eede et al. 2016a). These TPhP hydroxylated metabolites then undergo rapid conjugation through Phase II metabolism,[20] with either glucuronic acid or sulfate (Van den Eede et al. 2013). Glutathione conjugates have been detected using rat liver cell extracts (Chu and Letcher 2019). The glucuronic acid conjugates of 4-HO-TPhP, 3-hydroxyphenyl diphenyl phosphate (3-HO-TPhP) (Su et al. 2016), and 4-HO-DPhP have been detected in human urine (Bastiaensen et al. 2018).

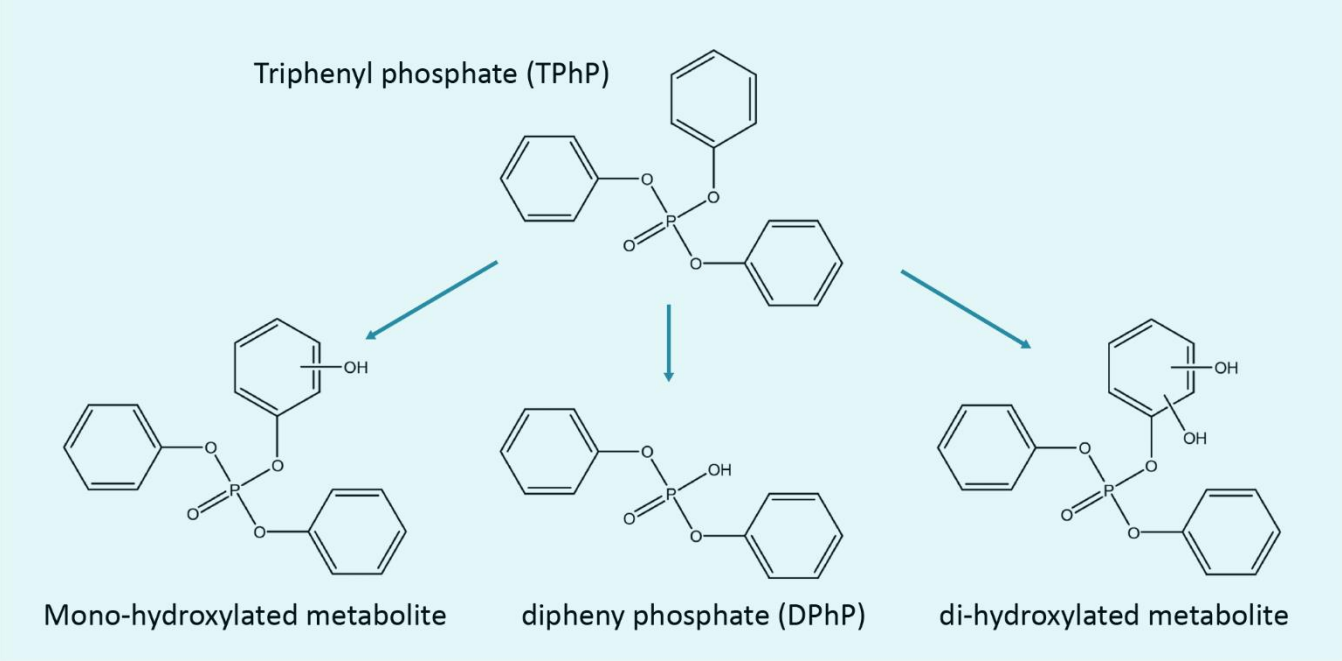


*Figure 2. Identified main water-soluble metabolites of TPhP in human liver microsomes (Zhang et al. 2018).*

In contrast, a study with human skin cell extracts found only DPhP as a metabolite, independent of CYP activity (Abdallah et al. 2019). The lack of the hydroxylated metabolites and the consistent formation rate of DPhP in the absence of the CYP cofactor NADPH lead Abdallah et al. (2019) to hypothesize that

[19] *A type of enzyme that cuts other molecules at ester bonds using water molecules in a reaction called hydrolysis.*

[20] *Phase II metabolism involves the addition of different larger compounds (conjugation) that includes glucuronic acid, glutathione, sulfate, etc. to increase the water solubility of the parent compound to facilitate excretion.*

metabolism in the skin may primarily involve carboxylesterases rather than CYPs. The skin is a portal of entry to the body; therefore, metabolism in the skin may limit dermal absorption of unmetabolized TPhP. TPhP has also been shown to undergo metabolism to DPhP in the blood (Van den Eede et al. 2016b; Wang et al. 2020b). However, the rate of TPhP metabolism in blood plasma is approximately 10 times slower than in liver tissue, indicating a minor role of metabolism in the blood in the disposition and clearance of TPhP from the body (Wang et al. 2020b).

In summary, TPhP metabolism in the liver results in a mixture of metabolites, with 4-HO-TPhP and DPhP as the predominant products. Hydroxylated metabolites, like 4-HO-TPhP, are further conjugated to glucuronic acid, sulfate, and glutathione. While the liver mainly generates these metabolites, human skin cells primarily produce DPhP. Metabolism of TPhP to DPhP also occurs in the blood. Metabolism of TPhP in other tissues, including the kidney, has not been measured. These studies indicate a complex profile of TPhP biotransformation pathways within the human body.

### 4.3.4. Excretion

Following exposure to TPhP and subsequent metabolism, DPhP is the primary metabolite detected in urine and, therefore, has been the primary target for measurement in biomonitoring studies (Wang et al. 2021b; Mendelsohn et al. 2016). Glucuronide conjugates of 4-HO-TPhP and 3-HO-TPhP have also been detected in urine but at lower frequencies and concentrations compared to DPhP (Su et al. 2016; Zhang et al. 2018). 4-HO-TPhP is thought to be a more specific biomarker of TPhP exposure, since DPhP is found in the environment (Tan et al. 2019; Liu et al. 2021b) and because DPhP is also the metabolic product of other organophosphate ester flame retardants to which people are exposed (Ballesteros-Gómez et al. 2015a; Ballesteros-Gómez et al. 2015b; Phillips et al. 2020). Glucuronide conjugates of 4-HO-DPhP have also been detected in urine at lower frequencies than DPhP, although at concentrations closer to that of DPhP (Bastiaensen et al. 2018; Zhao et al. 2019; Wang et al. 2020a). Phenyl phosphate (PhP), a possible metabolite of DPhP, was reported at low frequency and concentration in urine compared with DPhP in one human biomonitoring study (Reemtsma et al. 2011), while PhP was not detected in human liver cell metabolism studies (Van den Eede et al. 2013; Van den Eede et al. 2016a). Unmetabolized TPhP has been measured in the urine of people with kidney disease, although the amount detected did not correlate with measures of kidney function (Tsai et al. 2022). TPhP has also been measured in the urine of children in Taiwan (Chen et al. 2023).

Data gaps persist regarding the biliary and fecal excretion of TPhP and its metabolites and regarding whether there may be reuptake of excreted TPhP or its metabolites in the kidney or intestinal tract.

## 4.4. Degradation, reaction, or metabolic products of concern

*Reference: California Code of Regulations, title 22, section 69503.3(a)(1)(G). Reference: California Code of Regulations, title 22, section 69503.3(a)(1)(G).*

*A Candidate Chemical may degrade, form reaction products, or metabolize into other chemicals that have one or more hazard traits. These metabolites, degradation products, and reaction products (which may or may not be Candidate Chemicals) may cause different adverse impacts from those of the parent chemical. In some cases, a Candidate Chemical's degradation or reaction products or metabolites may have the same hazard trait, and may be more potent or more environmentally persistent, or both, than the parent chemical. In such cases, adverse impacts may be more severe, or may continue long after, the Candidate Chemical's release to the environment.*

As discussed in Section 4.3, TPhP is metabolized into several metabolites. DPhP is the primary metabolite found in urine and is used as an indicator of TPhP exposure in human biomonitoring studies (see Section 5.4). DPhP has been shown to cause liver toxicity in animal studies (see Section 4.5.1.1 for additional details).

## 4.5. Hazard traits and toxicological or environmental endpoints

*Reference: California Code of Regulations, title 22, section 69503.3(a)(1)(A).*

*The hazard traits and environmental or toxicological endpoints summarized in this section are defined in the SCP regulations sections 69501.1(a)(36) and (33), respectively, both of which refer to the Office of Environmental Health Hazard Assessment's (OEHHA) Green Chemistry Hazard Trait regulations (California Code of Regulations, Title 22, Chapter 54). These include exposure potential, toxicological, and environmental hazard traits.*

### 4.5.1. Toxicological hazard traits

Based on a review of the most recent authoritative reports and peer-reviewed literature, there is strong evidence that TPhP causes liver toxicity (hepatotoxicity). There is suggestive evidence that TPhP affects thyroid hormones (endocrine toxicity) and is a developmental, neurodevelopmental, and reproductive toxicant. The following summarizes DTSC's research findings supporting the identified hazard traits.

#### *4.5.1.1. Hepatotoxicity*

TPhP exposures in experimental animal studies result in liver effects, as evidenced by increased liver weight observed in short and subchronic exposure studies. A 2018 National Toxicology Program (NTP) study found dose-dependent increases in liver weight and elevated serum high density lipoprotein (HDL) cholesterol and total cholesterol in male rats orally treated with TPhP for 4 days (NTP 2018). The increased HDL cholesterol concentrations were reported as the most sensitive endpoint related to liver function (NTP 2018). The study also noted dose-dependent decreases in body weight. A short-term reproductive and developmental toxicity study conducted by NTP also showed increased liver weights in the parental female rats orally exposed to ≥ 3,000 ppm TPhP from gestation day 6 through postnatal day 28 (Witchey et al. 2022). ANSES (2019) and ECHA (2020) summarized an unpublished study,

conducted in accordance with the Organization for Economic Co-operation and Development (OECD) Test Guideline (TG) 408,[21] where six-week-old rats exposed to 1,500 and 7,500 ppm TPhP for 90 days exhibited increased liver weights, centrilobular liver cell hypertrophy (i.e., increase in the size of liver cells in the center of the liver lobules near the central vein), higher cholesterol levels, and reduced body weight gain. Male rats were more sensitive to the liver effects than female rats (ANSES 2019; ECHA 2020). Additionally, Sutton et al. (1960) reported increased liver weight in male rats treated with TPhP for 35 days in their feed.

DPhP exposures in mice have been shown to result in hepatoxic effects. A 12-week DPhP drinking water study in five-week-old female mice reported changes in liver metabolism, including alterations in lipid (i.e., fat) accumulation in the liver, and reduced body weight in comparison to control mice (Selmi-Ruby et al. 2020). In addition, expression of genes responsible for the breakdown of fat and its conversion into energy was decreased in DPhP-dosed animals (Selmi-Ruby et al. 2020).

#### *4.5.1.2. Endocrine toxicity*

Liver effects may consequently disrupt the production of hormones in the thyroid gland and alter circulating concentrations of thyroid hormones (Noyes et al. 2019). Six-week-old rats exposed to TPhP through their diet had bigger thyroid glands as evidenced by measured size and weight, and an increased incidence and/or severity of follicular cell hypertrophy[22] of the thyroid gland (ANSES 2019; ECHA 2020). In a study by NTP (2018), rats exposed orally for 4 days had dose-dependent decreases in free thyroxine (T4)[23] in blood serum. Furthermore, data from an NTP (2021) short-term reproductive toxicity study indicated that parental females exposed to TPhP orally had decreased serum triiodothyronine (T3) and free T4 at high TPhP doses.

In epidemiology studies of pregnant women, there is also some evidence that TPhP may change the blood levels of thyroid hormones (Yao et al. 2021; Choi et al. 2021a; Percy et al. 2021a). Choi et al. (2021a) collected urine from pregnant women at 17 weeks, which corresponds with the first trimester, when the fetus is dependent upon the mother entirely for thyroid hormones. The authors found that women with DPhP urine concentrations in the 75$^{th}$ percentile had an increased total T3 to total T4 ratio in blood when compared to pregnant women with DPhP concentrations in the 25$^{th}$ percentile. DPhP in maternal urine at delivery was associated with lower free T3 and total T4 and increased thyroid

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*[21] TG 408 is an OECD validated method for repeated dose 90-day oral toxicity study in rodents designed to provide information on health hazards likely to arise from exposure to a test substance via oral administration (OECD 2018).*

*[22] Follicular cell hypertrophy is when the cells that make up the thyroid gland wall increase in size and height.*

*[23] Thyroxine (T4) is the primary circulating thyroid hormone, which is converted to the more active hormone, triiodothyronine (T3) in tissues. Both T3 and T4 are transported in the body bound to other proteins. The free (unbound) hormones can enter cells.*

stimulating hormone (TSH)[24] in umbilical cord blood; no association was found for samples collected between 16 and 26 weeks of pregnancy (Percy et al. 2021a). Yao et al. (2021) reported that elevated DPhP levels in urine, collected randomly throughout pregnancy, were linked to an increase in maternal TSH levels in concurrently collected blood samples. In addition, maternal DPhP in urine showed a trend of higher TSH in newborn males (Yao et al. 2021). However, Tao et al. (2021) reported that DPhP in maternal urine collected in the third trimester was associated with lower TSH levels in the blood of newborn females. Overall, studies show that TPhP and possibly DPhP cause changes in thyroid hormones, but there is not a consistent increase or decrease in hormone production across the studies.

#### *4.5.1.3. Developmental toxicity*

Alterations in metabolism during critical life stages may have adverse impacts on health, such as changes in weight gain, fatty liver, and susceptibility to type 2 diabetes and other conditions, including metabolic syndrome (Heindel et al. 2017). Rat offspring perinatally exposed to high doses of TPhP (10,000 and 15,000 ppm), as noted by an NTP study, exhibited significantly smaller sizes compared to the control group (Witchey et al. 2022). TPhP treatment negatively impacted the number of live pups and offspring survival in comparison to control animals, with these effects potentially linked to maternal toxicity observed at the same doses (Witchey et al. 2022). In contrast to this work, low-dose exposures of TPhP to mice and rats in early life may lead to the development of obesity and metabolic dysfunctions in adult animals (Green et al. 2017; Wang et al. 2018; Wang et al. 2019b).

Wang et al. (2018) observed that male mice exposed subcutaneously to TPhP during infancy (postnatal day 1 through postnatal day 10) are more sensitive to some effects of TPhP exposures than females. Male mice exposed to low doses of TPhP (2 µg/day) had significant increased body weight gain in comparison to control mice at 12 weeks of age (Wang et al. 2018). Low oral doses of TPhP promoted body weight gain in male mice exposed during early life (i.e., gestational day 6 [*in utero*] to lactation day 21) (Wang et al. 2019b). When exposed to the highest dose of TPhP during gestation and lactation, and then fed a high fat diet after weaning, male mice had increased weight gain, fat accumulation, fatty liver, and insulin resistance later in life compared to mice on low fat diets or those not perinatally exposed to TPhP (Wang et al. 2019b).

Similarly, Green et al (2017) studied the effects of perinatal TPhP exposure in a type 2 diabetes mellitus rat model. As young adults, male and female offspring of pregnant rats orally exposed to 170 µg/day TPhP between gestational day 8 and postnatal day 21 had significantly higher body weights and increased mean weight of fat depots in comparison to controls, suggesting that TPhP intensifies the

[24] *TSH is produced in pituitary gland and stimulates the thyroid to produce thyroid hormones. High TSH is an indicator of insufficient thyroid hormones in the body.*

development of obesity (Green et al. 2017). This study also reported that the male offspring showed an accelerated onset of type 2 diabetes in comparison to weight-matched controls (Green et al. 2017).

TPhP-induced metabolic dysfunctions may also be sex specific. Adolescent mice exposed orally to TPhP for five weeks demonstrated sex-specific effects on the liver and metabolism (Wang et al. 2019a). Increased serum levels of triglycerides, total cholesterol, and HDL cholesterol, and decreased serum LDL cholesterol were seen in both TPhP-treated male and female mice (Wang et al. 2019a). However, female mice also had significantly increased blood serum levels of glucose and free fatty acids, increased glucose tolerance and insulin resistance, and significant lipid accumulation in the liver, indicating that females were more affected by TPhP exposures than males during puberty (Wang et al. 2019a).

In summary, timing and dose of TPhP exposures at different life stages may alter the rate of body weight gain, as well as sex specific metabolic dysfunction, and are suggestive lines of evidence for developmental toxicity.

#### *4.5.1.4. Neurodevelopmental toxicity*

Several studies in experimental animals and humans indicate that there may be some neurodevelopmental toxicity concerns associated with TPhP exposure. TPhP has been reported to cross the blood-brain barrier in zebrafish, mice, and rats (Wang et al. 2016; Liu et al. 2020; Witchey et al. 2022). Effects of TPhP on cholinesterase (a marker of acute neurotoxicity following organophosphate ester pesticide exposure) activity have also been reported in two NTP studies (NTP 2018; Witchey et al. 2022). NTP (2018) observed dose-dependent decreases in cholinesterase activity in the blood of rats exposed to TPhP. The 2022 NTP developmental toxicity study in rats (see Section 4.5.1.1) observed larger brains (55-126% larger than controls when exposed to ≥ 10,000 ppm TPhP) and dose-dependent reductions in the activity of acetylcholinesterase (AChE, an enzyme involved in regulating nerve transmission) and butyrylcholinesterase (BChE) in the brains and blood of the rat pups (Witchey et al. 2022). A significant sex difference in cholinesterase activity in the brain was observed, with male offspring exposed to TPhP having decreased levels compared to exposed females (Witchey et al. 2022).

Zebrafish exposed to TPhP as embryos showed alterations in behavior, such as reduced activity in response to changes in light conditions (Alzualde et al. 2018; Quevedo et al. 2019). Female rats orally exposed to TPhP from birth to postnatal day 28 lost the preference for male odor in comparison to controls, suggesting TPhP may disturb normal sexual behavior of female rats (Nakayama et al. 2020). Mice pups exposed to TPhP from postnatal day 10 to 70 showed dose-dependent decreases in the percentage of spontaneous altered behavior compared to controls, demonstrating spatial navigation and reference memory deficits in the TPhP-exposed groups (Zhong et al. 2021). This study also observed impaired learning and memory function in TPhP-treated animals (Zhong et al. 2021).

Some epidemiology studies have reported associations of DPhP in urine from pregnant women with cognitive or behavioral outcomes in their children (Castorina et al. 2017b; Doherty et al. 2019a; Choi et al. 2021b); while other studies have not (Doherty et al. 2019b; Liu et al. 2021a; Percy et al. 2021b; Hall et al. 2023; Ramos et al. 2023). One study reported an association of DPhP in children's urine and reduced cognitive ability, but the association was only observed for children with low socioeconomic status (Percy et al. 2022). Conversely, a small study found improved behavioral outcomes in young children associated with a 10-fold increase in TPhP concentration on handwipes (Sugeng et al. 2021). Overall, TPhP exposure may cause changes in cholinesterase activity, odor preference, behaviors including sexual behavior, learning, spatial navigation, and memory.

#### *4.5.1.5. Reproductive toxicity*

TPhP may affect the developing reproductive system in both male and female experimental animals. The Witchey et al. (2022) short term reproductive and developmental toxicity study observed dose-dependent delayed puberty in both male and female rat offspring perinatally exposed to TPhP. In the 15,000 ppm TPhP treatment groups, offspring failed to achieve balano preputial separation in males or vaginal opening in females (Witchey et al. 2022). Dose-dependent delays in vaginal opening and decreased total follicle number were also observed in female mice orally dosed with TPhP postnatally (starting from postnatal day 21) (Ma et al. 2021).

### 4.5.2. Exposure Potential hazard traits

#### *4.5.2.1. Transplacental or Lactational Transfer*

There is suggestive evidence of transplacental transfer of TPhP based on studies in humans and experimental animals. TPhP has been measured in human placenta (Ding et al. 2016), embryos (Zhao et al. 2017), and human cord blood (Wang et al. 2021b). In one human study, during the first eight weeks of pregnancy, TPhP was found to be transferred from the mother to the embryo and surrounding chorionic villi, although it could not be determined whether TPhP was present in both the embryo and chorionic villi or only one of the two (Zhao et al. 2017). During this phase of pregnancy, the placenta is still developing, and early pregnancy is a sensitive period for exposures to chemicals, including TPhP (Zhao et al. 2017). In another study, TPhP was measured in both maternal and umbilical cord blood at similar concentrations, indicating the transfer of TPhP to the fetus (Wang et al. 2021b). Additionally, CYP1A2-induced liver metabolism decreases during pregnancy may lead to increases in the half-life of TPhP in pregnant women which may increase TPhP exposure to the mother and fetus (Wang et al. 2021b).

Animal studies also provide evidence of transplacental transfer. Witchey et al. (2022) reported TPhP detections in gestation day 18 fetuses and postnatal day 4 offspring in a short-term reproductive study in rats. Baldwin et al. (2017) observed dose-dependent accumulation of TPhP in placentas associated

with male offspring, but not in placentas associated with female offspring, from pregnant animals orally dosed from gestational day 9 to 18.

There is suggestive evidence of lactational transfer of TPhP based on studies in humans and wildlife. TPhP has been detected at a mean concentration of 0.149 ± 0.146 ng/mL in 55 out of 100 breast milk samples collected in the U.S. (Ma et al. 2019). Kim et al. (2014) also reported median TPhP concentrations in breast milk samples from Japan, Vietnam, and the Philippines at 1.4, 4.9, and 19 ng/g lipid weight, respectively. In a study of a mass mortality event of dolphins from the Gulf of Mexico, researchers found TPhP that was approximately 10 times higher in the fat of nursing age dolphins than that of adult females, suggesting that lactational exposure may be an important exposure pathway for TPhP (Kuehl and Haebler 1995 as reviewed by OECD 2002).

Overall, studies suggest that transplacental and lactational transfers are important exposure pathways for TPhP. Please see Section 4.3.2. for additional information on TPhP distribution related to transplacental and lactational transfer.

# 5. POTENTIAL FOR EXPOSURES TO THE CANDIDATE CHEMICAL IN THE PRODUCT

*Reference: California Code of Regulations, title 22, section 69503.3(b).*

*The SCP regulations direct the Department to evaluate the potential for public or aquatic, avian, or terrestrial animal or plant organism exposure to the Candidate Chemical in the product by considering one or more factors for which information is reasonably available.*

## 5.1. Presence of the Candidate Chemical in the product

*Reference: California Code of Regulations, title 22, section 69503.3(b)(2).*

*This subsection summarizes available information indicating the Candidate Chemical's presence in and release from the product.*

TPhP is often used as a plasticizer in nail products to increase softness or flexibility and has been found at concentrations as low as 0.49% w/w and as high as 4.0% w/w, and at concentrations ranging from 0.000097% to 6.2% weight/volume (w/v) (Table 2). TPhP may also be present as a contaminant in nail products at concentrations up to 0.1% (Table 2). The frequent use of TPhP in nail products is indicated by data from the Cosmetic Ingredient Review (CIR) Panel and from the Mintel Global New Products Database (GNPD). (Mintel GNPD is a fee-for-service database that tracks consumer products launched globally.)

### *Summary of TPhP Concentration Data in Nail Products*

Available studies on TPhP concentrations in nail products are summarized in Table 2; TPhP concentrations varied from 0.49% to 4.0% w/w. Most of the studies in Table 2 only measured TPhP in nail polishes, although Estill et al. (2021) also detected TPhP in a top coat at a concentration of 2.5% w/w. More recently, DTSC detected TPhP in additional nail products, including polishes, hardeners, base coats, and UV gel polishes at concentrations ranging from 8,880 µg/mL to 46,100 µg/mL (0.88% w/v to 4.6% w/v) (DTSC 2023b). TPhP was also detected in bulk nail polishes sampled at four nail salons with concentrations ranging from 9.7 µg/mL to 62,000 µg/mL (0.000097% w/v – 6.2% w/v) (NIOSH 2019a). In DTSC's recent information call-in request to manufacturers, TPhP was reported as a contaminant at concentrations up to 0.1% in many products such as polishes, base coats, and primers, and as an intentional ingredient at concentrations ranging from up to 0.1% to 10% in products such as nail polishes and UV gel polishes (DTSC 2023a).

*Table 2. Summary of analytical studies measuring TPhP concentrations in nail products.*

| Location Sample Obtained | Product Type | Concentration Range or value in % | Percentage | Source |
|---|---|---|---|---|
| Salon in California | Nail Polish and Top Coat | 1.3 - 3.5 | By weight | (Estill et al. 2021) |
| Retail in North Carolina | Nail Polish | 0.49 - 1.7 | By weight | (Mendelsohn et al. 2016) |
| Japan | Nail Polish | 1.1 - 1.8[25] | By weight | (Tokumura et al. 2019) |
| Spain | Nail Polish | 4.0 | By weight | (Grau et al. 2019) |
| California Professional Retail | Nail Polish | 1.3 – 2.5[26] | By weight | (DTSC 2012) |
| Greater Boston Salons and Retail | Nail Polish | <LOD – 0.79[27] | By weight | (Young et al. 2018) |
| California Professional Retail and Retail | Multiple[28] | 0.88 – 4.6 | By volume | (DTSC 2023b) |

[25] *Three of the 45 products in which TPhP was detected were from U.S. manufacturers.*

[26] *Estimated concentrations.*

[27] *<LOD means the reported concentration was below the limit of detection (LOD).*

[28] *TPhP was detected in an anti-nail bite product, a base coat, gel polishes, hardeners, a top coat, and a UV gel polish. In this study, some products were categorized as multifunctional – intended to function as top coats, base coats, and hardeners, or as top coats and base coats.*

| Location Sample Obtained | Product Type | Concentration Range or value in % | Percentage | Source |
|---|---|---|---|---|
| Nail Salons[29] | Nail Polish | 0.00097 – 6.2 | By volume | (NIOSH 2019a) |
| Request to California Manufacturers | Multiple | Contaminant up to 0.1%; intentional ingredient ranging from 0.1 to 10% | Not specified[30] | (DTSC 2023a) |

### *Summary of TPhP Frequency Data Use in Nail Products*

A report by CIR (2018) found that TPhP was used in 331 nail products, with 286 being nail polishes and enamels. From January 2001 to December 2020, 26,244 nail products were available in the U.S. and 802 new or reformulated TPhP-containing nail coatings were released, 12 of which were marketed to children (Mintel 2023a). These TPhP-containing products include nail polish/lacquers, base coats, topcoats, and gel polishes (Mintel 2023b).

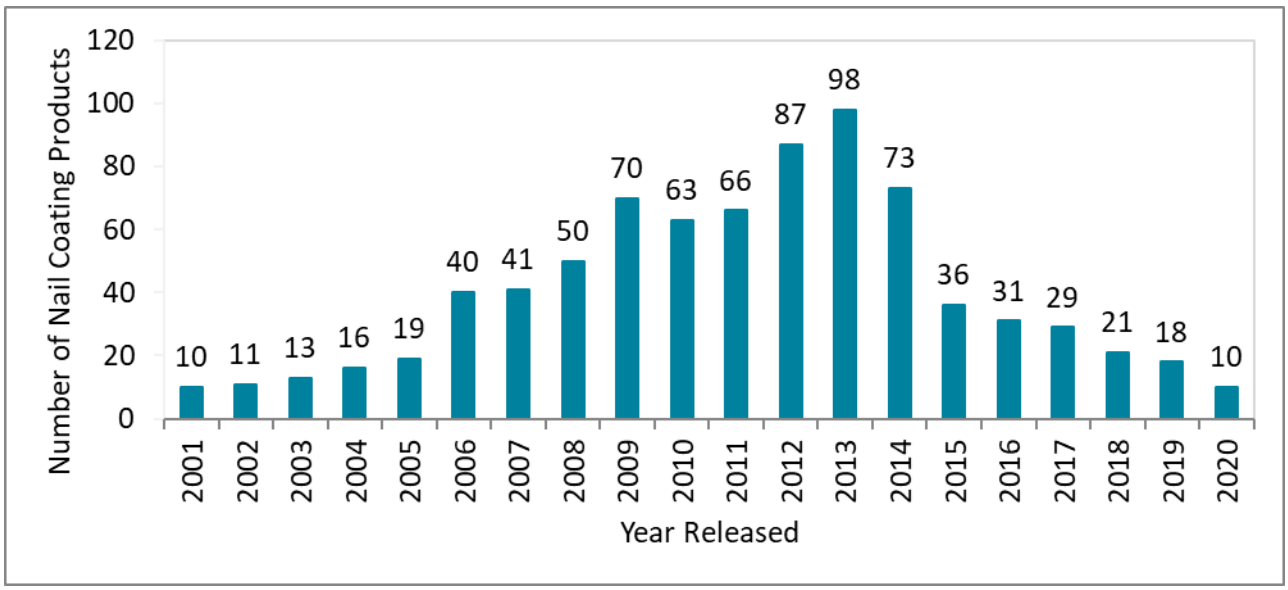


*Figure 3. Number of new or reformulated nail coatings containing TPhP released in the U.S. by year (Mintel 2023a).*

As seen in Figure 3, new or reformulated nail coatings introduced in the U.S. retail market increased from 2001 to 2013, peaking in 2013 (Mintel 2023a). 4.92% of the new or reformulated products in this time period contain TPhP (Mintel 2023a). Between 2015 to 2020, 2.47% of newly introduced products

[29] *Location not specified.*
[30] *Manufacturers did not provide units for concentration data in their submittals to DTSC.*

contained TPhP, indicating a decrease in the overall percentage of new TPhP-containing products in recent years.

### *Products reported in DTSC's Information Call-In*

In 2020, DTSC conducted an information call-in request from nail product stakeholders, including manufacturers, retailers, distributors, importers, assemblers, and trade associations, to gather information on chemicals that may be used as ingredients in nail products. Thirty-one companies responded to DTSC's request for information regarding chemicals used in formulations and products. Ingredients were reported for a total of 13,108 nail products of all types, 1,154 of which (9%) were reported to contain TPhP (Table 3), with the majority containing TPhP concentrations from 1% to 5% (DTSC 2023a). The product types reported in the information call-in that contained TPhP included base coats, gel or gel-like products, nail hardeners, primers/bonders/bond-aid products, topcoats, UV gel polish, water-based polish, and other nail products, with the majority being traditional nail polishes (Table 3) (DTSC 2023a).

*Table 3. Estimated total number of nail products compared to number of nail products containing TPhP by product type (DTSC 2023a).*

| Product type | Reported to contain TPhP products | Total products | By percentage |
|---|---|---|---|
| UV gel polish | 42 | 5551 | 0.7% |
| Water-based polish | 1 | 31 | 3.2% |
| Traditional nail polish | 1031 | 4410 | 23.3% |
| Top coat | 18 | 69 | 26.0% |
| Other (specify) | 46 | 182 | 25.3% |
| Gel polish/Gel-like polish (no UV required) | 2 | 2 | 100.0% |
| Base coat | 12 | 51 | 23.5% |
| Primers/ bonders/ bond-aid product | 1 | 24 | 4.1% |
| Hardeners | 1 | 7 | 14.3% |

## 5.2. Market presence and trends

*Reference: California Code of Regulations, title 22, sections 69503.3(b)(1)(A-C)*

*Product market presence information may be used to assess potential exposures to the Candidate Chemical in the product. This information may include statewide sales by volume or number of units, the intended use(s) of the product, and characteristics of the targeted customer base.*

The use of professional nail products, salon services, and consumer nail products have the potential to expose nail salon workers, patrons, and consumers to TPhP and other chemicals. In 2016, $8.53 billion was spent on professional nail services in the U.S. (Nails Magazine 2018). Further, more than $1.3 billion is spent annually in the U.S. on retail sales of nail products, with nail polish sales representing more than 33% of this amount (Drug Store News 2016). In California, there are 7,897 nail salons (Nails Magazine 2018) with 130,336 licensed manicurists (DCA 2017) and an additional 314,552 licensed cosmetologists (DCA 2018). According to one survey, 95% of U.S. nail salons offer nail polish services, 67% offer UV gels, and 82% offer nail art (Nails Magazine 2015).

In 2019, nail product sales were between $718.6 million and $2.3 billion (Marketline 2020; Mintel 2024a). This included approximately $552.5 million in nail coating sales and $152.2 million in nail treatment sales (Statista 2021a). Based on Nielsen data (Nielsen 2020), which accounts for approximately 90% of brick-and-mortar stores in California, [31] annual sales from October 2019 to October 2020 equaled:

- $83.5 million for nail polish and polish strips;
- $10.9 million for nail treatments; and
- $2 million for nail kits/sets.

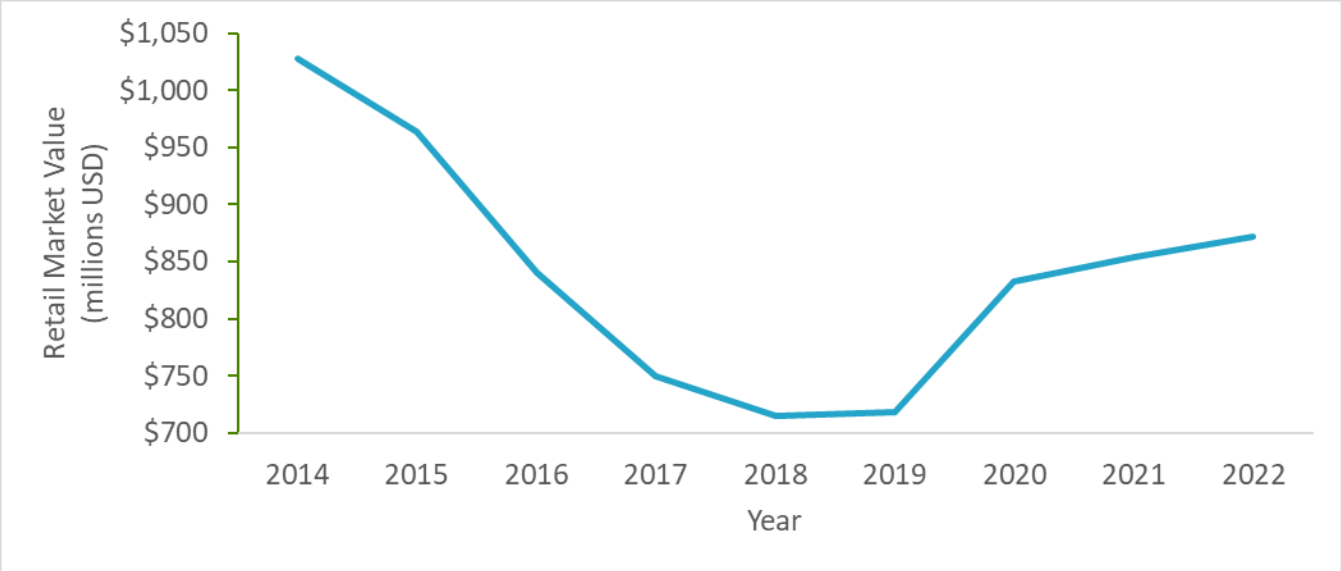


*Figure 4. Nail product retail market value in millions of US dollar by year (Mintel 2024b).*

[31] *DTSC's analyses and calculations are based, in part, on data reported by Nielsen, through its Syndicated Retail Measurement Scantrack Service, for nail products sold in California over a 52-week timeframe ending on October 3, 2020. The conclusions drawn from the Nielsen data are those of DTSC and do not reflect the views of Nielsen. Nielsen is not responsible for, had no role in, and was not involved in, analyzing and preparing the results reported herein.*

Online shopping has accelerated the use of nail products, with the U.S. nail products market growing from $715.3 million in 2018 to $718.6 million in 2019 (Figure 4). This is a reversal of downward trend in sales from 2014 to 2018 (Mintel 2024a). The nail products market grew between 2020 to 2022, from $832.7 million to $871.8 million. The trend toward online shopping increased significantly due to the COVID-19 pandemic. For instance, Amazon sales of nail products grew 218% between March and April of 2019 and the same period in 2020 (Gerstell et al. 2020).

## 5.3. Potential exposures to the Candidate Chemical during the product's life cycle

*Reference: California Code of Regulations, title 22, sections 69503.3(b)(3); 69503.3(b)(4)(A-H).*

*Potential exposures to the Candidate Chemical or its degradation products may occur during various product life cycle stages, including manufacturing, use, storage, transportation, waste, and end-of-life management practices. Information on existing regulatory restrictions, product warnings, or other product use precautions designed to reduce potential exposures during the product's life cycle may also be discussed here.*

Nail product consumers, salon workers, and salon patrons, may be exposed to TPhP through various routes, primarily dermal and inhalation. Dermal exposure can occur during activities such as applying TPhP-containing products without using protective gloves, both in professional salons and at home. Inhalation occurs when TPhP volatizes into indoor air during application of nail products, impacting both nail salon workers and patrons.

### 5.3.1. Use

The use of nail products containing TPhP is widespread in households and in salons. Salon workers experience daily exposures due to their nature of work, which can be exacerbated by their longer than average workdays and workweeks (Quach et al. 2008; Nails Magazine 2016). Nationally, there are approximately 69,738 nail salons with 393,581 licensed manicurists (Nails Magazine 2017). In California, there are 7,897 nail salons (Nails Magazine 2018) with approximately 130,000 licensed manicurists and 300,000 cosmetologists (DCA 2017; DCA 2018).

The frequency of consumer nail product application and removal varies, with some nail salon customers opting for a professional manicure every one to two weeks and self-applying a top coat every two to three days (Sally Beauty Supply 2017). Furthermore, some women may apply nail polish even more frequently at home (Berger et al. 2019). The frequency of other nail product services like gel nails and nail art varies.

As discussed in Section 4.3.1, dermal absorption is an important route for TPhP exposure during use of TPhP-containing nail products. Mendelsohn et al. (2016) measured elevated DPhP in the urine of

volunteers following application of nail polish containing TPhP. In another study, volunteers who applied nail polish containing 4% TPhP also had increased DPhP in their urine (Grau et al. 2019). Taken together, these two studies indicate that dermal absorption is a major route for TPhP exposure from nail products.

Inhalation may also contribute toward TPhP exposure when nail products containing TPhP are opened. Although TPhP has a low vapor pressure, there is still some potential for volatilization (see Section 4.1 for more details). Testing of opened nail products in use at nail salons in comparison with the same newly purchased product found much lower concentrations of TPhP, suggesting that TPhP is released from nail products to the surrounding environment through volatilization (NIOSH 2019a). Further, building parameters, air exchange rates, ventilation, weather conditions, seasonal variations (Grešner et al. 2016), and the use of Personal Protective Equipment (PPE) (Quach et al. 2013; OSHA 2017) can all affect TPhP exposure potential from nail products in the indoor environment. Ventilation is a critical factor in determining indoor air conditions and potential exposure to workers and consumers. While adequate ventilation reduces worker exposure, many salons do not have adequate ventilation (Roelofs and Do 2012; Goldin et al. 2014; NYDOH 2016).

A typical nail salon is often confined to a single room with one to 10 workstations or tables (Yang and Han 2010). These establishments are sometimes located within enclosed buildings, such as indoor malls (Quach et al. 2011). A nail technician sits on one side of a table facing a client on the other side. This proximity results in salon workers handling nail products close to their breathing zone, thereby exposing themselves and their customers to the chemicals in these products (Yang and Han 2010). Further, nail salons tend to be limited to small workspaces (for example, a mean area of 512 square feet in Alameda County, California) with inadequate ventilation, which could increase the magnitude of potential inhalation exposure (Quach et al. 2011).

Nail salon workers often work long hours and may be simultaneously exposed to multiple TPhP-containing nail products. The typical work duration for a nail salon worker is 36 or more hours per week, serving an average of 16 to 20 customers (Nails Magazine 2016). Approximately 10% of nail salon workers serve 36 or more customers per week (Nails Magazine 2016).

Nail products are also commonly used in homes in California. In the Study of the Use of Products and Exposure-Related Behaviors (SUPERB), one or more nail products were identified in 40% of homes in California with young children (Bennett et al. 2012).

The frequency of nail product use has also been measured through surveys of personal care product use, usually as part of biomonitoring and health studies (Lang et al. 2016; Berger et al. 2019). For example, in a study of 130 pregnant Canadian women, 7% reported they “always or often wear” nail polish, while 30% reported they sometimes wear nail polish (Lang et al. 2016).

A 2010 study of households across central and northern California found even more widespread use. Wu et al. (2010), collected data from 604 households over three consecutive annual phone interviews. Participants were females from three different age groups: children, their mothers, and women who were 55 or older (Wu et al. 2010). Table 4 provides a summary of the study's findings.

*Table 4. Nail product use among female participants (Wu et al. 2010).*

| Participant Type and Age (in years) | Number of Participants | Nail Polish (Self) User % | Nail Polish (Professional) User % |
|---|---|---|---|
| Adult < 55 | 374 | 53 | 81 |
| Adult > 55 | 99 | 39 | 77 |
| Child ≤ 5 | 185 | 45 | ---* |
| Child > 5 | 31 | 79 | ---* |

**No data was available for professional users under age 18.*

A higher percentage of the adult female participants in the 2010 study received professional nail services than applied nail polish themselves (Table 4) (Wu et al. 2010). Nail polish use was common among even the youngest study participants: 45% of girls age 5 and under and 79% of girls over age 5 used nail polish (Table 4) (Wu et al. 2010). This study also showed a correlation between use of nail products among parents and children in the same household, suggesting either that parents use nail products on their children in similar patterns as on themselves or that parental use patterns influence their children's use of nail products and, thus, their exposure to chemicals from the products (Wu et al. 2010).

### 5.3.2. Manufacturing, Storage, Transportation, End of Life

This Profile focused on the exposure to TPhP from nail products and associated potential adverse impacts related to product use. Therefore, exposure to TPhP during manufacturing, storage, transportation, and end of life of nail products was not evaluated.

## 5.4. Indicators of potential exposures to the Candidate Chemical

*Reference: California Code of Regulations, title 22, section 69503.3(b)(2).*

*The SCP regulations consider various data that indicate potential for exposure to the Candidate Chemical or its degradation products, including: monitoring data indicating the Candidate Chemical's presence in the indoor and outdoor environment, biota, humans (e.g., biomonitoring studies), human food, drinking water, and other media, as well as evidence of persistence, bioaccumulation, and lactational and transplacental transfer.*

Household and business monitoring data, environmental monitoring data, and human biomonitoring data all indicate the potential for exposure to TPhP. Household and business monitoring data and human exposure data are prioritized for discussion in this section since environmental exposure is not a key concern from nail product use (see Section 4.2 for information concerning environmental fate of TPhP).

Human exposure to TPhP in nail products, including for nail salon workers, is expected to result from direct contact with nail products. In addition, TPhP can be released from nail products into the indoor environment, albeit in potentially minor amounts, contributing to exposure via air and dust. TPhP and its metabolites reported in human blood, serum, and plasma were previously discussed in Section 4.3.1.

### 5.4.1. Monitoring data from nail salons

Exposure to TPhP in occupational settings is well documented. Additionally, available studies indicate that inhalation exposure to TPhP in nail salons is higher when compared to exposures in homes and other common indoor environments (Hammel et al. 2016; Kim et al. 2019; Estill et al. 2019; Nguyen et al. 2022). Median TPhP concentrations measured from active personal air samplers in the breathing zone of salon workers in two studies in the U.S. were 7.16 and 11.0 ng/m$^3$ (Estill et al. 2021; Nguyen et al. 2022). In contrast, median air concentrations collected from homes in Norway and the U.S. were 1.0 and 1.387 ng/m$^3$, respectively (Xu et al. 2016; Wang et al. 2019c). The median air concentration of samples collected from a mixture of residential, vehicle, and commercial indoor environments in the U.S. was 1.11 ng/m$^3$ (Kim et al. 2019). Table 5 summarizes studies that detected TPhP in nail salon indoor air.

*Table 5. Summary of studies that detected TPhP in the breathing zone air of nail salon workers.*

| Sample Type | Sample Location and Details | Number of Samples | Detection Frequency (%) | Range or Max, Concentration (ng/m3) | Median, Concentration (ng/m3) | Reference |
|---|---|---|---|---|---|---|
| Indoor air, 1 m above the ground | Albany, NY, Nail salon | 1 | 100 | 43.7 | N/A* | (Kim et al. 2019) |
| Personal breathing zone | California, 4 nail salons | 12 | 100 | 2.94 – 21.9 | 7.16 | (Estill et al. 2021) |
| Personal breathing zone | Toronto, Canada, 18 nail salons | 60 | 95 | 1.00 – 870 | 11.0 | (Nguyen et al. 2022) |

**Only one sample was measured.*

Passive sampling methods also indicate exposures to TPhP during nail salon workers' work shifts (Craig et al. 2019; Nguyen et al. 2022). Craig et al. (2019) conducted a pilot study in seven nail salons where 10 female nail salon technicians wore silicone wristbands on their wrists and pinned to their lapels throughout their shifts; TPhP was detected on wristbands located on the wrist and lapel (Craig et al. 2019). A larger Canadian study conducted by Nguyen et al. (2022) evaluated exposures to 45 nail salon technicians in 18 salons using a silicone wristband placed on their dominant hand and a silicone brooch attached near their breathing zone (Nguyen et al. 2022). There was a significant weak to moderate positive correlation between TPhP concentrations detected in air samples and either brooch or wrist band samplers. However, median concentrations of TPhP in the wristbands were 10 times higher than in the brooches, suggesting direct contact of the wristband with surfaces impacted with TPhP, and further suggesting that surfaces and surface dusts with TPhP in nail salons are another medium contributing to worker exposure (Nguyen et al. 2022).

### 5.4.2. Biomonitoring data from nail salon workers and nail product users

As previously discussed in Section 4.3.4, DPhP is the primary metabolite of TPhP and is, therefore, used as the target for evaluating exposure to TPhP in biomonitoring studies. Biomonitoring of nail salon technicians has been reported in two studies (Craig et al. 2019; Estill et al. 2021) (Table 6). Estill et al. (2021) collected pre- and post-work shift urine samples from 12 nail salon technicians from four San Francisco, California, nail salons. Nail salon workers' post-work shift urine samples had significantly more DPhP than pre-work shift samples (Estill et al. 2021). Estill et al. (2021) reported that the nail salon workers' post-shift urinary concentrations of DPhP were also significantly higher than those reported for the general U.S. population, for the U.S. population not born in the U.S., for non-Hispanic Asians, and for non-Hispanic Asians not born in the U.S. Craig et al. (2019) also collected pre- and post-work shift urine samples in the Boston area in a small pilot study of nail salon exposures. Geometric mean concentrations of DPhP in post-work shift urine samples were slightly elevated when compared to pre-work shift samples and to urine concentrations from other U.S. females from the National Health and Nutrition Examination Survey (NHANES) (Craig et al. 2019). Table 6 summarizes DPhP biomonitoring data from nail salons.

*Table 6. Summary of biomonitoring studies that measured DPhP in urine of nail salon workers.*

| Sample Location and Details | Number of Participants | Number of Samples* | Detection Frequency, % | | Concentration range, µg/g | | Geometric Mean Concentration, µg/g | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | Pre-Work shift | Post-Work shift | Pre-Work shift | Post-Work shift | Pre-Work shift | Post-Work shift | |
| Boston, MA, 7 nail salons | 10 | 20 | 90 | 90 | < 0.100 – 6.50 (CC) | < 0.100 – 4.10 (CC) | 1.10 (CC) | 1.30 (CC) | (Craig et al. 2019) |
| San Francisco, CA, 4 nail salons | 24 | 24 | 75 | 100 | 0.270 – 1.57 (CC) | 0.490 – 5.33 (CC) | 0.84 (CC) | 1.35 (CC) | (Estill et al. 2021) |

*CC = Creatinine corrected. Urine concentrations of DPhP normalized to the urine content of the metabolite creatinine. Creatinine correction is one method to control for varying dilution in urine in different samples.*

**Half of the samples were taken pre-shift and half were taken post-shift.*

In addition to the measurements of DPhP in nail salon workers, biomonitoring of volunteer users following nail polish application have demonstrated that nail products containing TPhP are a major source of DPhP in urine for nail polish users (Mendelsohn et al. 2016; Grau et al. 2019). Mendelsohn et al. (2016) demonstrated that application of nail polish containing TPhP (0.97% by w/w) caused a geometric mean seven-fold increase in urinary DPhP in volunteers measured 10-14 hours after application, and DPhP levels remained elevated for at least 24 hours (Mendelsohn et al. 2016). Similar findings were observed in four individuals whose urinary levels of DPhP were elevated 24 hours after application of nail polish containing TPhP (4% w/w) (Grau et al. 2019). Therefore, nail polish may be a significant source of TPhP exposure among nail polish users, especially for those who apply the product more frequently. The use of nail polish may also be one reason females typically have higher DPhP urine levels than males (Ospina et al. 2018; Wang et al. 2019e) (see Table 7). According to the 2013-2014 nation-wide National Health and Nutrition Examination Survey (NHANES) biomonitoring data, the adjusted geometric mean concentrations of DPhP in urine were significantly higher in females than in males for all age groups except for the 6 to 11-year-old age group (Ospina et al. 2018). Women were 3.6 times more likely to be above the 95$^{th}$ percentile of exposure (Ospina et al. 2018).

*Table 7. U.S. DPhP concentrations in urine from NHANES 2013-2014 (adapted from Ospina et al. 2018)*

| Compound | Population | Number of Samples | Range (µg/L) | Geometric Mean Concentration (µg/L) | 95th percentile |
|---|---|---|---|---|---|
| DPhP Unadjusted | U.S. (all) | 2,666 | < 0.16-193 µg/L | 0.845 | 6.23 |
| DPhP Creatinine Adjusted | 6-11 years old | 421 | ---** | *1.91 (males)<br>*2.25 (females) | 9.66 |
| | 12-19 years old | 427 | ---** | *0.91 (males)<br>*1.49 (females) | 6.59 |
| | 20-59 years old | 1,266 | ---** | *0.58 (males)<br>*0.95 (females) | 4.7 |
| | >60 years old | 552 | ---** | *0.52 (males)<br>*0.91(females) | 4.89 |

**Geometric mean concentrations (µg/L) are adjusted concentrations for creatinine, age, and sex.*
***No concentration range data was provided.*

### 5.4.3. Biomonitoring data from general population

Due to the ubiquitous nature of TPhP, its metabolites have been consistently measured in urine of the general population (Wang et al. 2021a). Exposure studies have linked DPhP in urine to indoor dust (Hoffman et al. 2015; Xu et al. 2019) and occupational exposures (Carignan et al. 2016; Estill et al. 2019). TPhP and DPhP have also been monitored in plasma, serum, and whole blood, but studies are limited and have mostly been performed in China, where DPhP levels in urine are much lower than the U.S. (Yang et al. 2020). With the exception of Australia, the U.S. population has the highest detected levels of DPhP in urine among all countries studied (Wang et al. 2021a).

Tables 7 and 8 summarize DPhP levels in the urine of the general U.S. population, including detections in sensitive populations of California. Although the range of exposures is highly variable, DPhP detection frequencies in the urine are high (79.4-100%), indicating nearly universal exposure to TPhP.

*Table 8. Summary of other biomonitoring studies that measured DPhP in urine in the general population.*

| Compound | Sample Location | Population | Number of Samples | Detection Frequency, % | Concentration, Range (µg/L) | Concentration, Median (µg/L) | Reference |
|---|---|---|---|---|---|---|---|
| DPhP (SGC) | California, U.S. | Mothers | 28 | 100 | 0.390 – 3.50 | 1.20 | (Butt et al. 2016) |
| | | Children ages 24 to 70 months | 33 | 100 | 0.360 – 82.0 | 2.50 | |
| DPhP (SGC) | Washington, U.S. | Children ages 15 to 18 months | 21 | 100 | 0.810 – 16.6 | 2.71 | (Thomas et al. 2017) |
| DPhP (SGC) | California, U.S. | Pregnant Women, 2nd trimester, low income, mostly Mexican-American | 310 | 79.4 | <0.33 – 54.3 | 0.93 | (Castorina et al. 2017a) |
| DPhP (SGC) | California, U.S. | Women, 2nd trimester, low Income | 132 | 99 | <0.2 – 112 | Not reported | (Varshavsky et al. 2021) |

*SGC = Specific Gravity Corrected. Urine concentration of a chemical normalized to the specific gravity (density) of the urine. SGC is one method to control for varying dilution in urine in different samples.*

Some studies with repeated measures of DPhP in urine collected over many months or years have observed that DPhP concentrations are highly variable during pregnancy (Percy et al. 2020), in young children (Yang et al. 2023), and in adults (Preston et al. 2017). Therefore, epidemiology studies based on single urine samples may not correctly characterize exposure over longer periods. To address this high degree of variability, repeated sampling of DPhP in urine is now more commonly performed (Yang et al. 2023), or other biomarkers of exposure are being measured, such as TPhP blood levels (Yang et al. 2020). Although other TPhP metabolites are also being measured in urine, they are, to date, less suitable biomarkers, due to lower frequencies of detection (see discussion in Section 4.3.4). Alternate biomarkers of exposure may be able address the problem that DPhP in urine could be the result of exposure to sources other than TPhP (Wang et al. 2021a).

### 5.4.4. Evidence of lactational transfer

Lactational transfer is considered an exposure potential hazard trait and is therefore discussed in section 4.5.2.1.

## 5.5. Aggregate effects

*Reference: California Code of Regulations, title 22, section 69503.3(a)(1)(B) and sections 69503.3(b)(3).*

*Multiple sources of exposure to the Candidate Chemical may increase the potential for significant or widespread adverse impacts.*

In addition to its use in nail products, TPhP is primarily used as a flame retardant in many consumer products, including electronics such as electrical power boards, electrical adaptors, heat sealers, televisions, and printers (CPSC 2015a). TPhP has been found in the foam of baby products such as car seats, changing table pads, and portable crib mattresses, as well as household furniture such as couches (Ionas et al. 2014; CPSC 2015b). Because of its ubiquitous use as a flame retardant in consumer products, there is a high potential for aggregate exposure to TPhP above that experienced directly from use of nail products alone, furthering the potential for significant or widespread adverse impacts.

Use of these consumer products may contribute to TPhP in indoor dust or air, especially from products made with treated plastics (CPSC 2015a). The major source of TPhP in dust is thought to come from its uses as a flame retardant as discussed above (Stapleton et al. 2009). After being released from products, TPhP can potentially adhere to household dust, leading to ingestion, or it can become airborne and be inhaled (CPSC 2015a). Two studies measured TPhP in the diet, in indoor air, in floor and surface dust, and in hand-wipes (Xu et al. 2016; Xu et al. 2019). Ingestion of indoor dust was determined to be the major source of TPhP exposure (Xu et al. 2016; Xu et al. 2019). TPhP air concentrations have been measured in homes, offices, cars, and various public places, with concentrations ranging from non-detectable to 1,000 ng/$m^3$ (CPSC 2015a).

Additionally, people in certain occupations, including chemical manufacturing, electronic scrapping, carpet installing, and spray polyurethane foam installation, may be further exposed to TPhP (Estill et al. 2019) in addition to exposures to TPhP in nail products.

Furthermore, the intake of food and water may also contribute to aggregate exposure to TPhP. A market survey conducted by FDA between 1982 and 1991 detected TPhP in 234 food items, including caramel, margarine, and baby food, at levels ranging from 0.02 to 0.04 ppm (CPSC 2015a). TPhP has also been detected in various water sources, including surface waters, groundwaters, and drinking waters in the U.S., with concentrations ranging from non-detectable to 7,900 ng/L (CPSC 2015a).

Further details regarding the environmental fate of TPhP upon release to the environment can be found in Section 4.2.

# 6. POTENTIAL FOR SIGNIFICANT OR WIDESPREAD ADVERSE IMPACTS

*Reference: California Code of Regulations, title 22, section 69503.2(a).*

*This section integrates the information provided in the Profile to demonstrate how the key prioritization principles, as identified in the SCP regulations, are met.*

DTSC has determined that exposure to TPhP through use of nail products may contribute to or cause significant or widespread adverse impacts to people in California, including sensitive subpopulations such as nail salon workers, pregnant people, and children. This determination is based on the potential for dermal and inhalation TPhP exposure in nail salons and at home, the evidence of exposure to TPhP based on biomonitoring and nail salon data, and the hazard traits associated with TPhP. Additionally, there may be cumulative exposure to other chemicals of concern used as ingredients in nail products such as toluene and methyl methacrylate.

Nail products and professional/pedicure services, which may expose nail salon workers and customers to TPhP, are very popular. In the U.S., there are approximately 69,738 nail salons with 393,581 licensed manicurists (Nails Magazine 2018), and in California there are 7,987 nail salons with approximately 130,000 licensed manicurists and 300,000 cosmetologists (DCA 2017; DCA 2018; Nails Magazine 2018). The primary exposure route by which nail salon workers and customers may be exposed to TPhP from nail products is through dermal contact, with inhalation potentially contributing as well (Mendelsohn et al. 2016; Estill et al. 2021; Nguyen et al. 2022). Oral exposure is also possible, particularly for breastfeeding infants of mothers using nail products, who may be exposed to TPhP via breastmilk (Kim et al. 2014; Beser et al. 2019; Ma et al. 2019). Building size, ventilation, and air exchange rates affect the indoor salon concentration of TPhP and the level of inhalation exposure for customers and nail salon workers (Quach et al. 2011; Grešner et al. 2016). Further, studies have detected TPhP concentrations in indoor nail salon air at levels higher than those found in homes (Xu et al. 2016; Nguyen 2021; Estill et al. 2021). Additionally, TPhP-containing nail products may be a source of short-term and chronic exposure for nail salon workers and nail product users (Mendelsohn et al. 2016).

Nail salon workers' exposure to TPhP is exacerbated by several factors including longer workdays and workweeks than employees in other sectors (Quach et al. 2008), and the use of and exposure to multiple TPhP-containing nail products. Additionally, nail salon spaces are confined and often lack proper ventilation, which increases the magnitude of potential inhalation exposure. Further, inadequate use of PPE, such as applying TPhP-containing nail products without gloves, may increase the possibility of dermal exposure (White et al. 2015; Mendelsohn et al. 2016).

As illustrated by the data and information described in this Profile, DTSC has determined that there is exposure to TPhP from nail products and that this exposure may cause or contribute to significant or widespread adverse effects.

## 6.1. Adverse impacts linked to the Candidate Chemical's hazard traits

*Reference: California Code of Regulations, title 22, section 69503.3(a).*

*The SCP Regulations direct DTSC to evaluate the potential for the Candidate Chemical to contribute to or cause adverse impacts by considering several adverse impact factors for which information is reasonably available.*

TPhP causes liver toxicity in experimental animals resulting in body weight and metabolic activity changes. There is also evidence of endocrine toxicity due to effects on thyroid hormones. Research studies suggest that TPhP is a developmental, neurodevelopmental, and reproductive toxicant (see Section 4.5.1 for additional information).

## 6.2. Populations that may be adversely impacted

*Reference: California Code of Regulations, title 22, section 69503.3(a).*

*This section identifies specific populations of humans and environmental organisms that may be harmed if exposed to the Candidate Chemical in the product. Sensitive subpopulations, environmentally sensitive habitats, endangered and threatened species, and impaired environments in California have special consideration, as they may be more vulnerable.*

Most nail product purchasers and users in the U.S. are female (Nails Magazine 2018). They come from various age groups, and many belong to sensitive subpopulations such as nail industry workers, infants, children, adolescents, and pregnant women (and their fetuses) (Wu et al. 2010; Ford 2014). More than 60% of female nail salon customers are of childbearing age (Figure 5).

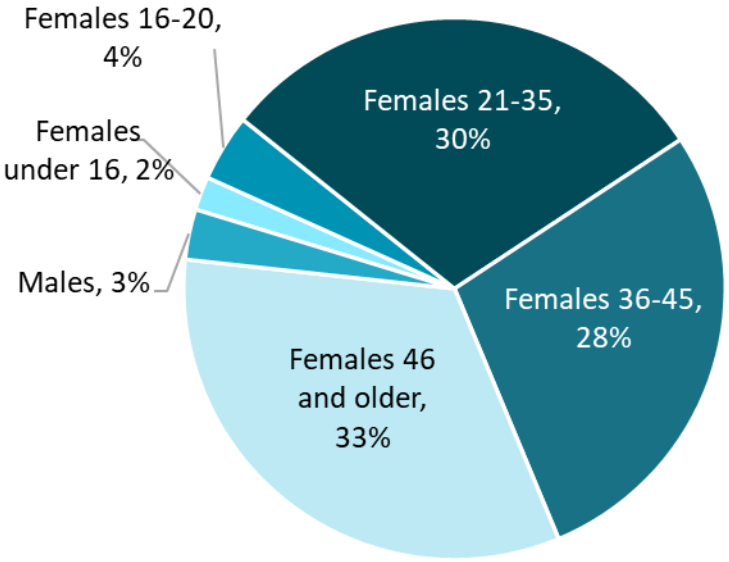


*Figure 5. Demographic makeup of nail salon customers (Nails Magazine 2017).*

Nail salon workers are an important sensitive subpopulation. Quach et al. (2008) estimate that 59% to 80% of nail salon workers in California are of Vietnamese descent. According to the U.S. Census Bureau, 90% of all nail salons in California are minority-owned and 68% are Vietnamese-owned (U.S. Census Bureau 2012). Additionally, U.S. nail salon workers are predominantly low-income and non-native English speaking women of childbearing age (Ford 2014; Nails Magazine 2017). Nail salon workers often have longer workdays and workweeks than employees in other sectors (Quach et al. 2008). They are often not provided with adequate information concerning chemical safety; they are often not provided with proper PPE (Quach et al. 2013); and their workplaces often lack appropriate ventilation (Quach et al. 2008). Furthermore, pregnant nail salon workers and their fetuses are especially sensitive to adverse impacts of TPhP exposure from nail products. Evidence indicates that there is transplacental transfer of TPhP from the mother to the developing fetus and that TPhP is a neurodevelopmental and developmental toxicant (see section 4.5 for additional information on transplacental transfer and hazard traits). Also, infants and children of nail salon workers often accompany their parents to the workplace and may be exposed to TPhP-containing nail products.

In summary, nail salon workers' potential for exposure to TPhP is exacerbated by several factors: long work hours; inadequate access to PPE and information concerning chemical safety; and workplaces lacking appropriate ventilation. As a result, nail salon workers are likely to experience higher exposures and adverse impacts to TPhP than the general population (see Section 5.3).

# 7. OTHER REGULATORY PROGRAMS

*Reference: California Code of Regulations, title 22, section 69503.2(b)(2).*

DTSC has assessed all applicable state and federal laws and regulations and international treaties or agreements with the force of domestic law related to nail products or TPhP in nail products and has identified the regulatory programs and laws described below related to TPhP, which are intended to protect public health and the environment. DTSC has determined that none of these programs overlaps or conflicts with its proposal to list nail products containing TPhP as a Priority Product, nor with any subsequent regulation that may result from such listing. Further, we are aware of no other pending regulatory actions currently addressing TPhP in nail products.

## 7.1. U.S. Food and Drug Administration

The U.S. Food and Drug Administration (FDA) is authorized by the Federal Food, Drug, and Cosmetic Act (FDCA) to oversee the safety of food, drugs, and cosmetics (21 CFR 701 2016). The FDCA does not authorize the FDA to require safety testing of cosmetics, and there is no approval process for cosmetic products prior to sale in the U.S. (except for color additives). However, the FDA can and does inspect cosmetics manufacturing facilities to ensure that cosmetics are not adulterated (21 CFR 701 2016).[32]

While cosmetic product manufacturers are legally responsible for ensuring the safety of their products, neither the FDCA nor FDA regulations require specific tests to demonstrate the safety of individual products or ingredients, and manufacturers are not required to share their safety information with the FDA. However, the FDA can pursue enforcement action against products on the market that it determines are not in compliance with the FDCA or the Fair Packaging and Labelling Act (FPLA), or against firms or individuals who violate these laws (21 CFR 701 2016).

## 7.2. Federal Food, Drug, and Cosmetic Act

The FDCA is a set of laws passed by Congress in 1938 giving authority to the FDA to oversee the safety of food, drugs, and cosmetics (FDA 2018a). The FDCA defines cosmetics as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body … for cleansing, beautifying, promoting attractiveness, or altering the appearance" (21 CFR 701 2016). As noted above, the FDA does not pre-approve cosmetic products. However, cosmetic products must be properly labeled and safe for consumers under labeled or typical conditions of use. The FDCA prohibits the marketing of adulterated or misbranded cosmetics in interstate commerce, and the FDA can

[32] *"Adulterated" cosmetics refers to product composition violations, whether they result from ingredients, contaminants, processing, packaging, or shipping and handling (FDA 2016). FDA Authority Over Cosmetics: How Cosmetics Are Not FDA-Approved, but Are FDA-Regulated. U.S. Food and Drug Administration (FDA).https://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074162.htm Accessed October 2017.*

remove cosmetics from the market that contain a "poisonous or deleterious substance which may render it injurious to users" or that are mislabeled (FDA 2018b).

## 7.3. Fair Packaging and Labelling Act

The Fair Packaging and Labelling Act (FPLA), a federal law, requires each package of household consumer products marketed or sold in the U.S. to bear a label that includes a statement identifying the commodity (eg. detergent, sponges, etc.); the name and place of business of the manufacturer, packer, or distributor; and the net quantity of contents in terms of weight, measure, or count (in both metric and English units). The FPLA is designed to facilitate value comparisons and to prevent the unfair or deceptive packaging and labelling of many household consumer commodities (FDA 2009).

## 7.4. California Professional Cosmetics Labeling Law

The California Professional Cosmetics Labeling Law requires that all professional cosmetic products manufactured on or after July 1, 2020, and sold in California, must meet all labeling requirements for any other cosmetic pursuant to the federal Food, Drug, and Cosmetic Act and the federal Fair Packaging and Labeling Act (Health and Safety Code Section 110371).

## 7.5. U.S. Environmental Protection Agency

The Toxic Substances Control Act (TSCA) of 1976 was enacted by Congress to test, regulate, and screen all chemicals produced in or imported into the U.S. TSCA requires any chemical that reaches the consumer marketplace to be tested for possible toxic effects prior to commercial manufacture (U.S. EPA 2015). At this time, the hazards for TPhP are currently being evaluated by the United States Environmental Protection Agency (U.S. EPA) under TSCA (U.S. EPA 2020b).

## 7.6. U.S. Occupational Safety and Health Administration

The Occupational Safety and Health Act requires employers to provide their employees with a place of work free from recognized hazards that cause or are likely to cause death or serious physical harm (29 USC Ch 15), such as exposure to toxic chemicals, excessive noise levels, mechanical dangers, heat or cold stress, or unsanitary conditions (U.S. EPA 2020b).

In 1970, the Occupational Safety and Health Administration (OSHA) set a permissible exposure limit (PEL) for TPhP of 3 $mg/m^3$ in air averaged over an eight-hour workday (29 CFR 1910). OSHA acknowledges that many of its PELs are outdated and inadequate to ensure the protection of employee health (OSHA 2021). Most of OSHA's PELs were issued shortly after the adoption of the Occupational Safety and Health Act in 1970 and have not been updated since (OSHA 2009).

Nevertheless, changes to occupational exposure limits are not among the regulatory response options DTSC might eventually impose for TPhP-containing nail products.

## 7.7. California Division of Occupational Safety and Health

TPhP is listed as a hazardous substance by the California Division of Occupational Safety and Health (Cal/OSHA) (8 CCR 339). Pursuant to Cal/OSHA's hazard communication regulations, employers must "provide information to their employees about the hazardous chemicals to which they may be exposed, by means of a hazard communication program, labels, and other forms of warning, Safety Data Sheets, and information and training" (8 CCR 5194).

TPhP is listed as an airborne contaminant (8 CCR 5155). Cal/OSHA has set a PEL for TPhP at 3 $mg/m^3$ (average concentration permitted over an eight-hour work shift) (8 CCR 5155).

## 7.8. California Department of Public Health, California Safe Cosmetics Program

The California Department of Public Health (CDPH) created the California Safe Cosmetics Program (CSCP) in response to the passage of the California Safe Cosmetics Act. Beginning in 2009, cosmetic manufacturers with aggregate sales greater than $1 million must report to CSCP products they sell in California that have intentionally added chemical ingredients identified as known or suspected carcinogens or reproductive or developmental toxicants by authoritative bodies (CDPH 2016). TPhP must be reported to CSCP if it is an ingredient in a cosmetic product (CDPH 2020).

While the intention of the Safe Cosmetics Act is to improve access to information about potentially harmful ingredients in cosmetics and to influence the reformulation of some products toward safer alternatives, it does not duplicate the SCP Regulations. The Safe Cosmetics Act requires manufacturers to report certain chemical ingredients in products, but it does not require manufacturers to evaluate those products for safer chemical alternatives.

## 7.9. California Air Resources Board

Under the Health and Safety Code section 44321 (HSC 44321 2003), the California Air Resources Board (CARB) is required to compile and maintain a list of substances that must be reported under the AB 2588 Air Toxics Hot Spots Program. TPhP is listed on the in the Hot Spots list of substances (CARB 2022). The Hot Spots Program requires stationary sources to report the types and quantities of listed substances released routinely into the air (CARB 2021).

# 8. POTENTIAL ALTERNATIVES

*Reference: California Code of Regulations, title 22, section 69503.2(b)(3).*

*This section summarizes information available to DTSC regarding alternatives that may or may not be safer than the Candidate Chemical. DTSC does not need to ensure that these alternatives are safer and may summarize their associated hazards to illustrate readily available information. The sections below may include information such as how readily available an alternative is, product functions addressed by the alternative, and implications for manufacturers using the alternative (e.g., use limitations, product reformulation, different equipment needs).*

Multiple chemical alternatives to TPhP were identified by a recent Mintel GNPD search and during DTSC's most recent nail products lab study (Mintel 2022b; DTSC 2023b). These potential chemical alternatives, their relevant hazard traits, and their use frequency in nail products are summarized below.

## 8.1. Sucrose benzoate, CAS RN 12738-64-6

Sucrose benzoate functions as a plasticizer and film former in cosmetic products (EC 2022a). The Environmental Working Group's (EWG's) Skin Deep cosmetics database (EWG Skin Deep) identified sucrose benzoate in eight nail coatings and three nail treatments (EWG 2022a). Scott et al. (2021) states that sucrose benzoate occurs in nail products at a concentration of up to 14.3%. Further, DTSC's nail products lab study found sucrose benzoate on the ingredient label of four products categorized as nail polish, top coat, or multifunctional (DTSC 2023b). Mintel GNPD lists 95 nail products containing sucrose benzoate entering the U.S. market as new or reformulated products from 2011-2021 (Mintel 2022b). ECHA identifies no hazards associated with sucrose benzoate exposure (ECHA 2022a), and sucrose benzoate is not on DTSC's Candidate Chemical (CC) List.

## 8.2. Ethyl tosylamide, CAS RN 1077-56-1/80-39-7

Ethyl tosylamide acts as a plasticizer and a film former in cosmetic products (EC 2022b). Ethyl tosylamide is the International Nomenclature Cosmetic Ingredient (INCI) name for N-ethyl-o-toluenesulfonamide (CAS RN 1077-56-1) and N-ethyl-p-toluenesulfonamide (CAS RN 80-39-7).

EWG Skin Deep identified N-ethyl-o-toluenesulfonomide as an ingredient in 13 nail polishes and two nail treatment products (EWG 2022b). In a limited nail lab study conducted in 2011, DTSC found that N-ethyl-o-toluenesulfonamide was the third most common plasticizer detected in nail products tested. It was detected in three of 14 nail lacquers at concentrations of 6,500 to 15,000 ppm (0.6 to 1.5% w/w) (DTSC 2012). As part of DTSC's 2023 nail products lab study, DTSC found N-ethyl-o-toluenesulfonamide on the ingredient labels of four nail polishes, two hardeners, and one multifunctional nail product (out of 156 total products) (DTSC 2023b). Additionally, Mintel GNPD identifies 166 nail products containing N-ethyl-o-toluenesulfonamide entering the U.S. market from 2011-2021 (Mintel 2022c). While N-ethyl-o-toluenesulfonamide is not on DTSC's CC list, according to ECHA, N-ethyl-o-toluenesulfonamide may be toxic to the skin and harmful if ingested (ECHA 2024b).

In two separate nail products lab studies, DTSC detected N-ethyl-p-toluenesulfonamide in one nail lacquer and one gel polish at concentrations of 5,300 ppm (0.5% w/w) and 1,678 ppm (0.2% w/w),[33] respectively (DTSC 2012; DTSC 2023b). EWG Skin Deep identifies N-ethyl-p-toluenesulfonamide as an ingredient in 13 nail polishes and two nail treatment products (EWG 2022b). Although N-ethyl-p-toluenesulfonamide is not on DTSC's CC List, according to ECHA, N-ethyl-p-toluenesulfonamide may cause skin, eye, and respiratory irritation (ECHA 2024c).

## 8.3. Acetyl tributyl citrate, CAS RN 77-90-7

Acetyl tributyl citrate, another plasticizer in use, is an odorless liquid that is soluble in most organic solvents. Nail products have been reported to contain concentrations of acetyl tributyl citrate up to 7.0%, with base coat and undercoat concentrations ranging from 4 to 6%, and nail polish and enamel products concentrations ranging from 0.8 to 7% (CIR 2002). According to EWG Skin Deep, acetyl tributyl citrate is mostly found in nail polishes and nail treatments, with the highest frequency in nail polishes (684 nail polishes compared to 21 nail treatments) (EWG 2022c). Additionally, Mintel GNPD lists 1,067 nail products containing acetyl tributyl citrate entering the U.S. market from 2011-2021 (Mintel 2022d).

Although it is not on DTSC's CC List, acetyl tributyl citrate can cause dermal toxicity, ocular toxicity, and neurotoxicity based on animal studies (CIR 2002). Acetyl tributyl citrate is also associated with ovarian toxicity, endocrine disruption, and neurotoxicity (Rasmussen et al. 2017; Qadeer et al. 2022).

## 8.4. Trimethylpentanediyl dibenzoate, CAS RN 68052-23-3

Trimethylpentanediyl dibenzoate is a plasticizer found in cosmetics (EC 2022c). EWG Skin Deep shows that trimethylpentanediyl dibenzoate is mostly found in nail coatings as compared to other nail products such as nail treatments (249 nail coatings compared to five nail treatments) (EWG 2022d). Mintel GNPD lists 402 nail products containing trimethylpentanediyl dibenzoate entering the U.S. market between 2011-2021 (Mintel 2022e).

According to a screening assessment by Environment and Climate Change Canada (ECCC), trimethylpentanediyl dibenzoate does not have any hazard traits of concern (ECCC 2019) and it is not on DTSC's CC list.

## 8.5. Trimethyl pentanyl diisobutyrate, CAS RN 6846-50-0

*[33] DTSC's recent nail products lab study did not distinguish between the two different isomers of ethyl tosylamide and only reported the concentration for ethyl tosylamide.*

Trimethyl pentanyl diisobutyrate functions as a plasticizer in nail products. EWG found trimethyl pentanyl diisobutyrate in 187 nail coatings, 19 nail treatments, and one nail glue (EWG 2022e).

Although it is not on DTSC's CC List, the Consumer Product Safety Commission (CPSC), found that trimethyl pentanyl diisobutyrate may be a moderate dermal toxicant based on animal studies in which exposure led to slight erythema (CPSC 2018a; ECHA 2022b). Slight erythema was also reported in a human study after 1% (v/v) trimethyl pentanyl diisobutyrate was dermally applied to 201 volunteers (CPSC 2018a). Additionally, trimethyl pentanyl diisobutyrate is considered to be a potential developmental toxicant, as evidenced by decreased litter size and litter weight in rat pups following maternal exposure from diets containing trimethyl pentanyl diisobutyrate concentrations of 1.5, 4.5, and 15 mg/g (ECHA 2022b). Further, the GHS classification system identifies trimethyl pentanyl diisobutyrate as a category 2 reproductive toxicant (ECHA 2022b).

## 8.6. Sucrose acetate isobutyrate, CAS RN 126-13-6

Sucrose acetate isobutyrate, another plasticizer, is used because of its compatibility with other nail coating ingredients such as resins, solvents, and other plasticizers. As a result, sucrose acetate isobutyrate allows for better adhesion of nail coatings to the natural nail. Sucrose acetate isobutyrate can also act as a fragrance fixer (ECCC 2020). EWG identifies sucrose acetate isobutyrate in 208 nail coatings, and six nail treatment products (EWG 2022f).

In a recent screening assessment, ECCC did not identify any hazard traits associated with exposure to sucrose acetate isobutyrate, which led to the conclusion that sucrose acetate isobutyrate is unlikely to adversely impact human health (ECCC 2020). Further, sucrose acetate isobutyrate is not on DTSC's CC List.

## 8.7. Tosylamide/epoxy resin, CAS RN 70-55-3

Tosylamide/epoxy resin is a yellow liquid with low water solubility (NICNAS 2013). Exposure to tosylamide/epoxy resin in nail products occurs when tosylamide/epoxy resin is present at concentrations up to 7.5% (NICNAS 2013). EWG found tosylamide/epoxy resin in 68 nail polishes and 13 nail treatment products (EWG 2022g). In DTSC's 2012 nail study, tosylamide/epoxy resin was detected in two nail polishes and one base coat (DTSC 2012). Additionally, Mintel GNPD identifies 359 nail products that entered the U.S. market from January 2011 to December 2021 (Mintel 2022f).

While tosylamide/epoxy resin is not on DTSC's CC List, animal skin treatments demonstrated slight erythema and edema[34] following tosylamide/epoxy resin skin exposure, which lasted for more than 72

[34] *Swelling caused by excess fluid trapped in the body's tissues.*

hours and resolved in seven and ten days, respectively (NICNAS 2013); thus, this compound may cause dermal effects.

## 8.8. Camphor, CAS RN 76-22-2

Many products such as coating products, polishes, and waxes include camphor as a plasticizer ingredient (ECHA 2021a). EWG Skin Deep Cosmetics database identifies camphor in 15 nail polishes, nine nail treatment products, and one nail glue (EWG 2022h). In DTSC's 2012 lab study, camphor was detected in 11 of 25 nail products, mostly in nail coatings (DTSC 2012). More recently, DTSC found camphor on the ingredient labels of 16 of 157 nail products (DTSC 2023b).

Although not on DTSC's CC List, camphor can be inhaled, absorbed dermally or ocularly, and ingested (NIOSH 2019b). In nail products, the most likely exposure routes are inhalation and dermal, and inhalation may result in effects to the respiratory system. Additionally, adverse effects may occur to the nervous system; therefore, camphor is a dermal toxicant, respiratory toxicant, and a neurotoxicant (NIOSH 2019b; Ferreira et al. 2020). As a result, the National Institute for Occupational Safety and Health (NIOSH) and OSHA set a reference exposure limit and PEL, respectively, of 2 mg/m$^3$ for inhalation toxicity (NIOSH 2019b).

## 8.9. Tosylamide/Formaldehyde Resin (TSFR), CAS RN 25035-71-6

Tosylamide/Formaldehyde Resin (TSFR) can function as a plasticizer and film former in cosmetic products (EC 2022d). EWG Skin Deep identifies TSFR in seven nail polishes, four nail treatment products, and one nail glue (EWG 2022i). Although DTSC only found TSFR on the ingredient labels of two products evaluated in the recent lab study, TSFR was reported in DTSC's information call-in in 40 nail products, including 25 solvent-based nail polishes and 7 UV gel polishes (DTSC 2023a; DTSC 2023b). Additionally, Mintel GNPD identifies 121 nail products containing TSFR entering the U.S. market from January 2011 to December 2021 (Mintel 2022f).

Although TSFR is not on DTSC's CC List, TSFR may contain free formaldehyde present in trace amounts (Engelhardt and Klinkner 1985; Sainio et al. 1997). Therefore, the primary hazard trait is dermal toxicity, as evidenced by allergic contact dermatitis due to the presence of formaldehyde (Yokota et al. 2007; Lazzarini et al. 2008). Formaldehyde (CASRN 50-00-0) is on DTSC's CC List. Formaldehyde is a respiratory toxicant, ocular toxicant, dermal toxicant, carcinogen, hepatotoxicant, and gastrointestinal toxicant (ATSDR 2010; ECHA 2017; OEHHA 2019). Occupational exposure to formaldehyde results in dermal irritation and allergic contact dermatitis in patch testing (ATSDR 2010; ECHA 2017; OEHHA 2019). Due to its respiratory effects, the World Health Organization (WHO) set an air quality guideline value for formaldehyde of 0.1 mg/m$^3$ in 2001 (ATSDR 2010; ECHA 2017; OEHHA 2019). Formaldehyde causes nasopharyngeal cancer in humans based on epidemiological evidence and also leads to weight changes and stress effects in the liver (Hauptmann et al. 2004; ATSDR 2010).

## 8.10. Diisobutyl adipate, CAS RN 141-04-8

Diisobutyl adipate is a colorless liquid and widely used plasticizer (CPSC 2019). EWG Skin Deep identifies diisobutyl adipate in four nail treatment products and two nail polishes (EWG 2022j). DTSC's information call-in request reported diisobutyl adipate in five nail products, classified either as a nail polish, top coat, base coat, UV gel top coat, or nail treatment (DTSC 2023a).

While not on DTSC's CC List, diisobutyl adipate is associated with kidney toxicity, although an increase in kidney weight was observed in rats only at the highest doses (no observed adverse effect levels (NOAEL) of 1,000 mg/kg-day) (CPSC 2019). Diisobutyl adipate may cause slight skin irritation based on a skin test in rabbits (CPSC 2019).

## 8.11. Isosorbide dicaprylate/caprate, CAS RN 1215036-04-6

Isosorbide dicaprylate/caprate is derived from a mixture of caprylic acid, capric acid, and isosorbide (EC 2022e). EWG Skin Deep identifies isosorbide dicaprylate, but not isosorbide caprate, as an ingredient in five nail coatings (EWG 2022k). According to DTSC's information call-in, isosorbide dicaprylate/caprate was reported in nine nail products including base coats, top coats, gel polish, and solvent-based nail polishes (DTSC 2023a). Additionally, Mintel GNPD lists 43 nail products containing isosorbide dicaprylate/caprate entering the U.S. market from 2011 to 2021 (Mintel 2022g).

While isosorbide dicaprylate/caprate is not on DTSC's CC List, it was found to induce hyperlocal sensitization in mice ears, but only on a single mouse, and overall was not found to be a skin sensitizer or irritant (ECHA 2021b).

## 8.12. Tributyl citrate, CAS RN 77-94-1

In cosmetic products, tributyl citrate functions as a solvent, plasticizer, or as a film-forming chemical (EC 2022f). EWG found tributyl citrate in six nail polishes (EWG 2022l). According to DTSC's information call-in, tributyl citrate was found in four nail polishes, one base coat, one nail primer, one gel polish, and one cuticle cream (DTSC 2023a). While not on DTSC's CC List, tributyl citrate can cause ocular toxicity (NIH 2021b). No hazard traits were identified by ECHA (ECHA 2022c).

## 8.13. Diethylhexyl adipate, CAS RN 103-23-1

Diethylhexyl adipate has multiple functions in cosmetics, including as a plasticizer, solvent, skin conditioner, and film former (EC 2021). EWG Skin Deep identifies diethylhexyl adipate in 16 nail coatings (EWG 2022m). Furthermore, DTSC's information call-in identified diethylhexyl adipate in three nail polishes and one top coat (DTSC 2023a).

Diethylhexyl adipate causes dermal and respiratory toxicity and is also a reproductive and developmental toxicant (NJDOH 1988; U.S. EPA 1992). Reproductive and development effects were noted in multiple rat studies (NJDOH 1988; U.S. EPA 1992). In acute dermal studies in rabbits, the median lethal dose (LD50) ranged from more than 8,670 to 16,300 mg/kg; however, no study details were available (CPSC 2018b). Diethylhexyl adipate is on DTSC's CC list.

## 8.14. Triacetin, CAS RN 102-76-1

Triacetin functions as a preservative, plasticizer, or solvent in cosmetics (CIR 2003). In cosmetic products, triacetin is found at concentrations between 0.8% and 4% (CIR 2003). EWG Skin Deep identifies triacetin in 12 nail coatings, one nail glue product, and one nail treatment (EWG 2022n). DTSC's recent lab study and information call-in identified triacetin in one nail polish and top coat (DTSC 2023a; DTSC 2023b). Additionally, Mintel GNPD identifies 11 nail products containing triacetin entering the U.S. market from January 2011 to December 2021 (Mintel 2022h).

Triacetin may contain carcinogenic 1,2-glyceryl esters as a contaminant. While ester chains longer than two carbons generally promote cell growth and proliferation, the specific structure of 1,2 glyceryl esters does not appear to promote cell growth and tumor promotion when present in triacetin (CIR 2003). More recent research indicates that structure, dose, and exposure pathway play a role in the ability of 1,2-glyceryl esters to promote tumors (CIR 2022). Triacetin has been identified as a dermal and ocular toxicant, with testing resulting in ocular irritation, such as burning, pain, redness, and change in corneal thickness in rabbit and human studies (CIR 2003). No additional observed damage or injury to the eye was detected (CIR 2003). Neither triacetin nor glyceryl esters are listed on DTSC's CC List. Qadeer et al. (2022) suggests that triacetin may be considered a "safe alternative."

## 8.15. Dibutyl phthalate, CAS RN 84-74-2

Dibutyl phthalate (DBP) is another plasticizer that is used in nail products (Young et al. 2018). Although DBP was not detected in DTSC's recent lab study, it was reported in DTSC's information call-in as a residual or contaminant in nine solvent-based nail polishes, one remover, one top coat, two base coats, one gel polish, one gel top coat, one primer, one UV base and top coat, and one UV gel polish (DTSC 2023a; DTSC 2023b). DBP is on DTSC's CC List. DBP causes reproductive, developmental, respiratory, endocrine, and hepatoxicity (DTSC 2024).

## 8.16. Dimethyl adipate, CAS RN 627-93-0

In cosmetic products, dimethyl adipate can be used as a plasticizer, emollient, and skin conditioner (EC 2022g). EWG found dimethyl adipate in 37 nail polish removers (EWG 2022o). DTSC's recent information call-in reported dimethyl adipate in one nail polish remover (DTSC 2023a). In addition,

Mintel GNPD lists three nail products containing dimethyl adipate entering the U.S. market from January 2011 to December 2021 (Mintel 2022i).

While dimethyl adipate is not on DTSC's CC List, dimethyl adipate can cause ocular and respiratory toxicity (NIEHS 2016; NIH 2021c). ECHA lists dimethyl adipate as an eye irritant 2,[35] although no study details were identified (ECHA 2022d). Exposure to inhaled dimethyl adipate may cause adverse effects to the respiratory system as demonstrated by inhalation studies with rats (NIEHS 2016).

## 8.17. Di(2-ethylhexyl)phthalate (DEHP) (CAS RN 117-81-7) and p,p'-1,3-phenylene p,p,p',p'-tetraphenyl ester phosphate [PBDPP] (CAS RN 57583-54-7)

Nail products may contain more than one chemical functioning as a plasticizer. Young et al. (2018) detected one phthalate plasticizer, di(2-ethylhexyl)phthalate (DEHP), and one organophosphate ester plasticizer, p,p'-1,3-phenylene p,p,p',p'-tetraphenyl ester phosphate (PBDPP), also known as resorcinol bis(diphenyl phosphate)), at low concentrations in nail products. However, the concentrations of DEHP and PBDPP were greater than 100 ppm in individual nail products, indicating that these two chemicals were likely intentionally added as secondary plasticizers rather than as incidental contaminants in the products (Young et al. 2018). The possible use of secondary plasticizers as demonstrated by Young et al. (2018) may indicate that other plasticizers may have less favorable functional characteristics. Both DEHP and PBDPP are on DTSC's CC List. DEHP is a carcinogen and a developmental and reproductive toxicant. PBDPP is designated as a Priority Chemical under Biomonitoring California.

# 9. ADDITIONAL CONSIDERATIONS

*This section summarizes other relevant information not captured under the adverse impacts and exposure factors named in section 69503.3 of the Safer Consumer Products regulations.*

## 9.1. California Programs Addressing Nail Product Safety

In California, several efforts seek to address nail product safety. In 2012, San Francisco's Department of the Environment created a voluntary Healthy Nail Salon recognition program[36] for nail salons that use safer chemical alternatives in nail products, train their employees on safer practices to minimize chemical exposure, provide and require employees to use PPE, and install ventilation units to improve indoor air quality (SF Environment 2012). Since 2012, other counties and cities in California have

[35] *Chemicals identified as an eye irritant 2 have the potential to induce reversible eye irritation (ECHA 2022d).*

[36] *This predated the creation of DTSC's Healthy Nail Salon Recognition Program in 2017. See section 9.2.1 for additional details on this program.*

established voluntary healthy nail salon programs that recognize nail salons for promoting nail product and employee safety, similar to the San Francisco voluntary recognition program (CHNSC 2021).

## 9.2. California Laws

In addition to the voluntary recognition programs established by local jurisdictions, there are also California laws that seek to address the health, safety, and education of nail salon workers. These are briefly summarized below.

### 9.2.1. The Healthy Nail Salon Recognition Program (Health & Safety Code Section 25257.2)

The Healthy Nail Salon Recognition Program, established in 2017, recognizes nail salons that use nail polishes and nail polish removers that contain fewer toxic chemicals and improve ventilation. It provides guidelines, created by DTSC, for use by local jurisdictions to implement voluntary healthy nail salon programs, including a list of chemicals that should not be used by nail salons seeking program recognition.

### 9.2.2. Barbering and Cosmetology: Labor Law Education Requirements (Business & Professions Code Sections 7312, 7314, 7314.3, 7337, 7347, and 7389)

The Barbering and Cosmetology Labor Law Education Requirements provide for improved education and language access for nail salon workers.

### 9.2.3. Barbering and Cosmetology: Establishments: Posting Notice (Business & Professions Code Section 7353.4)

The Barbering and Cosmetology Establishments Posting Notice requires nail salons to post notices regarding workplace rights along with wage and hour laws in English, Spanish, Vietnamese, and Korean.

### 9.2.4. California Professional Cosmetics Labeling Law (Health & Safety Code, Section 110371)

The California Professional Cosmetics Labeling Law requires manufacturers to disclose ingredients on the label of professional cosmetics. This law makes the violation of its provisions a crime. The law also authorizes CDPH to require cosmetic labels to list ingredients for professional cosmetics. Professional cosmetic products manufactured on or after July 1, 2020, and available for sale in California, must have a label affixed on each container that satisfies all the labeling requirements.

## 9.3. Other States' Laws

Other states, including New York, have sought to address nail salon worker safety. In 2015, New York state enforced new ventilation requirements for nail salons (Watkins 2021). This enforcement was the

result of an exposé by the New York Times, which described the inadequate working conditions and "labor law violations that nail salons face" (Watkins 2021).

## 9.4. International Laws and Regulations

### 9.4.1. European Union

TPhP is registered under the European Union Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Regulation. TPhP is currently undergoing assessment regarding its endocrine disrupting activity (ECHA 2021c). TPhP was on the 2017 Community Rolling Action Plan (CoRAP); the CoRAP is a process that prioritizes the evaluation of substances in the EU[37]/EEA[38] over a three-year period with the intention to investigate the risk posed by a chemical to human health or the environment (ECHA 2021c). In their documents for selecting TPhP, grounds for concern included suspected endocrine disruption, wide dispersive use, consumer use, and aggregated tonnage (ECHA 2013).

## 9.5. Pending Legislation

The Campaign for Safe Cosmetics, which is an initiative by Breast Cancer Prevention Partners, recently introduced two bills to the U.S. Congress related to nail product and salon safety -- the Cosmetic Safety Protections for Communities of Color and Salon Workers Bill and the Cosmetic Supply Chain Transparency Act (BCPP 2024a; BCPP 2024b).

Briefly, the Cosmetic Safety Protections for Communities of Color and Salon Workers Bill would federally mandate (BCPP 2024a):

- access to translated safety data sheets;
- funding for research grants to identify chemicals of concern and health impacts from cosmetics and personal care products used by these communities;
- funding for the development of green chemistry safer alternatives; and
- creation of a Center of Excellence on Cosmetic Safety for Communities of Color and Salon Worker Health and Safety to share data and generate solutions to the toxic exposures experienced by these sensitive populations.

The Cosmetic Supply Chain Transparency Act would federally mandate upstream suppliers such as fragrance houses, formulating labs, suppliers of ingredients, suppliers of finished products, and suppliers of raw materials to provide brand owners with ingredient disclosure, toxicity, safety data, and certificates of analyses for beauty and personal care products. If passed, this law would also levy

[37] *EU = European Union*
[38] *EEA = European Economic Area*

penalties on suppliers that do not provide required information within 90 days of brand owners' requests (BCPP 2024b).

## 10. CONCLUSIONS

DTSC has determined that nail products containing TPhP meet the key prioritization criteria for listing a Priority Product (CCR, title 22, section 69503.2(a)):

1. There are potential public and/or aquatic, avian, or terrestrial animal or plant organism exposures to TPhP and its metabolite DPhP from nail products; and

2. There is a potential for one or more of these exposures to contribute to or cause significant or widespread adverse impacts.

TPhP is frequently used as a plasticizer in nail products, including nail coatings, nail art, and nail and cuticle treatments. While the primary exposure pathway to TPhP from nail products is dermal, inhalation and oral exposure can occur as well.

The use of nail products is widespread in California and thus there is potential for considerable exposure of TPhP. There are 7,897 nail salons and approximately 130,000 licensed manicurists in California. More than $1.3 billion is spent annually in the U.S. on retail sales of nail products, with nail polish sales representing over 33% of this amount.

Nail salon exposure studies have measured TPhP in indoor salon air and in the personal breathing space of nail salon workers, which has been found to be higher than in homes. Further, one study demonstrated that nail coatings may be a source of short-term and chronic exposure to TPhP in nail salon workers and frequent users of nail coatings.

Nail salon workers have been shown to have higher urinary level of DPhP, than the general population. DPhP is the main urinary metabolite of TPhP.

In addition to the evidence of potential exposure, there is also potential for TPhP to cause adverse impacts. There is strong evidence that TPhP exhibits liver toxicity (hepatotoxicity). There is suggestive evidence that TPhP exhibits endocrine, developmental, neurodevelopmental, and reproductive toxicity.

Chemical exposure to TPhP among salon workers is an issue of environmental injustice and inequity as a large majority of nail salon workers are of Vietnamese descent and of lower socioeconomic status. As a sensitive subpopulation, these workers are at greater risk of adverse effects when exposed to TPhP in nail products. They often work more than eight hours a day or 40 hours per week and lack essential chemical safety information, adequate PPE, and proper workplace ventilation, exacerbating their exposure and potential risks. Additionally, other parameters such as building size and air exchange

rates may affect the indoor salon concentration of TPhP and, consequently, the level of inhalation exposure to nail salon workers.

Pregnant nail salon workers and their fetuses are especially sensitive to adverse impacts of TPhP exposure from nail products due to transplacental transfer of TPhP from the mother to the developing fetus. Infants and young children are particularly vulnerable to the adverse effects of TPhP due to physiological differences. Compounding this issue, infants and children of nail salon workers are frequently present at the salons and may be exposed to TPhP-containing nail products. Even if not directly exposed to TPhP-containing nail products, nursing infants and young children may ingest TPhP through breastmilk.

Further studies may help inform DTSC's future decision-making. Nevertheless, there is sufficient information regarding potential exposures and adverse impacts from nail products containing TPhP to designate nail products containing TPhP as a Priority Product.

## 11. ACRONYMS AND ABBREVIATIONS

**Abbreviations used in this document:**

| | |
|---|---|
| AA | Alternatives Analysis |
| AAT | Alternatives Analysis Threshold |
| ANSES | French Agency for Food, Environmental and Occupational Health & Safety |
| ATSDR | Agency for Toxic Substances & Disease Registry |
| CAS | Chemistry Abstract Service |
| Cal/OSHA | California Division of Occupational Safety and Health |
| CARB | California Air Resources Board |
| CC List | Candidate Chemicals List |
| CCR | California Code of Regulations |
| CDPH | California Department of Public Health |
| CFR | Code of Federal Regulations |
| CHNSC | California Healthy Nail Salon Collaborative |
| CIR | Cosmetic Ingredient Review |
| CoRAP | Community Rolling Action Plan |
| CPSC | Consumer Products Safety Commission |
| CSCP | California Safe Cosmetics Program |
| DBP | Dibutyl phthalate |
| DCA | California Department of Consumer Affairs |
| DEHP | Di(2-ethylhexyl) phthalate |
| DPhP | Diphenyl phosphate |
| DTSC | Department of Toxic Substances Control |
| EC | European Commission |

| | |
|---|---|
| ECCC | Environment and Climate Change Canada |
| ECHA | European Chemicals Agency |
| EEA | European Economic Area |
| EU | European Union |
| FDA | U.S. Food and Drug Administration |
| FDCA | Federal Food, Drug, and Cosmetic Act |
| FID | Flame Ionization Detector |
| FPD | Flame Photometric Detector |
| FPLA | Fair Packaging and Labelling Act |
| GC | Gas Chromatography |
| GHS | Globally Harmonized System of Classification and Labeling of Chemicals |
| GNPD | Mintel Global New Products Database |
| GPC | Global Product Classification |
| LC | Liquid Chromatography |
| LED | Light-emitting diode |
| MS | Mass Spectrometry |
| NICNAS | National Industrial Chemicals Notification and Assessment Scheme |
| NIEHS | National Institute of Environmental Health Sciences |
| NIOSH | National Institute for Occupational Safety and Health |
| NHANES | National Health and Nutrition Examination Survey |
| NOAEL | No observed adverse effect levels |
| NTP | National Toxicology Program |
| OECD | Organization for Economic Co-operation and Development |
| OEHHA | Office of Environmental Health Hazard Assessment |

| | |
|---|---|
| OH-DPhP | Hydroxy-Diphenyl Phosphate |
| OPFR | Organophosphate Flame Retardant |
| OPPTS | Office of Prevention, Pesticides and Toxic Substances |
| ORCHARD | Origins of Child Health and Resilience in Development |
| OSHA | U.S. Occupational Health and Safety Administration |
| 4-HO-DPhP | 4-Hydroxyphenyl phenyl phosphate |
| 3-HO-TPhP | 3-Hydroxyphenyl-diphenyl phosphate |
| 4-HO-TPhP | 4-Hydroxyphenyl-diphenyl phosphate |
| PBDPP | p,p'-1,3-phenylene p,p,p',p'-tetraphenyl ester phosphate |
| PEL | Permissible Exposure Limit |
| PPE | Personal Protective Equipment |
| PPN | Priority Product Notification |
| PQL | Practical Quantitation Limit |
| REACH | Registration, Evaluation, Authorization and Restriction of Chemicals |
| REL | Reference Exposure Limit |
| ROMA | Risk Management Option Analysis |
| SCP | Safer Consumer Products |
| SF Environment | San Francisco Department of the Environment |
| SGC | Specific gravity corrected |
| SUPERB | Study of Use of Products and Exposure-Related Behaviors |
| STEL | Short Term Exposure Limit |
| TPhP | Triphenyl phosphate |
| TSCA | Toxic Substances Control Act |
| UV | Ultraviolet |

| | |
|---|---|
| U.S. EPA | United States Environmental Protection Agency |
| U.S. | United States |

**Units used in this document:**

| | |
|---|---|
| kg/L | Kilogram per liter |
| Koa | Octanol-air partition coefficient |
| Koc | Soil adsorption coefficient |
| Kow | Octanol-water partition coefficient |
| $mg/cm^2$-hr | Milligram per cubic centimeter hour |
| mg/kg | Milligram per kilogram |
| mg/kg bw/day | Milligram per kilogram body weight per day |
| mg/kg-day | Milligram per kilogram day |
| mg/L | Milligram per liter |
| $mg/m^3$ | Milligram per cubic meter |
| mol/L | Mol per liter |
| ng/g dw | Nanogram per gram dry weight |
| ng/g | Nanogram per gram |
| ng/g ww | Nanogram per gram wet weight |
| ng/L | Nanogram per liter |
| $ng/m^3$ | Nanogram per cubic meter |
| ng/mL | Nanogram per milliliter |
| $pg/m^3$ | Picogram per cubic meter |
| ppb | Parts per billion |
| ppm | Parts per million |

| | |
|---|---|
| µg | Microgram |
| µg/g | Microgram per gram |
| µg/mL | Microgram per milliliter |
| v/v | Volume per volume |
| w/v | Weight per volume |
| w/w | Weight per weight |

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# APPENDIX A: POTENTIAL RELEVANT FACTORS

**Non-exhaustive list of adverse impact factors that may be relevant to this proposed Priority Product**

Relevant Factors are used in SCP's Alternatives Analysis (AA) to make a focused and meaningful comparison of adverse impacts during the product's lifecycle between the Priority Product (PP) and alternative. This Profile has identified potential adverse impacts in the following categories:

- Adverse public health impacts
- Environmental fate
- Physicochemical properties
- Associated exposure pathways and life cycle segments
    - Use

**At a minimum**, all AAs submitted for this product-chemical combination must include a discussion of the potential adverse impacts listed above and how they compare between the Priority Product and the alternative(s), including their degradation products, that have been identified at the appropriate point in the lifecycle. This list is not intended to be comprehensive. Also, alternatives evaluated in the AA Report will likely have additional adverse impacts that do not apply to the Priority Product; these will also need to be assessed in the AA Report. Product performance and economics are generally not evaluated in the Profile.

# APPENDIX B: REPORT PREPARATION

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# APPENDIX C: ALTERNATIVES ANALYSIS THRESHOLD RATIONALE

## Alternatives Analysis Threshold Explanation

Section 69505.3 of title 22 of the California Code of Regulations states that when a Chemical of Concern is present in a Priority Product at or below the Alternatives Analysis Threshold (AAT), the manufacturer of the Priority Product may be exempt from submitting an Alternatives Analysis (AA) if it instead submits an AAT Notification by the due date for the Preliminary AA Report. Section 69501.1(a)(12) defines the AAT as either the Practical Quantitation Limit (PQL) or some higher value specified by the Department of Toxic Substances Control (DTSC). The PQL is defined as "the lowest concentration of a chemical that can be reliably measured within specified limits of precision and accuracy using routine laboratory operating procedures" (California Code of Regulations, title 22, section 69501.1(a)(52).) Further, DTSC must set an AAT if a Chemical of Concern occurs solely as a contaminant in a Priority Product. However, even if a Chemical of Concern is present as contaminant, if its concentration in the Priority Product exceeds the AAT, the manufacturer must submit a Priority Product Notification (PPN) and either 1) a Preliminary and then Final Alternatives Analysis report (CCR, Title 22, section 69505.1) or 2) one of these notifications (CCR, Title 22, section 69505.2):

- Chemical Removal Intent and Confirmation Notifications;
- Product Removal Intent and Confirmation Notifications; or
- Product-Chemical Replacement Intent and Confirmation Notification

## Alternatives Analysis Threshold Value

DTSC proposes to set the AAT for TPhP in nail products at 250 parts per million (ppm).

Several studies, including one by DTSC, analyzed the presence of TPhP in nail products, as discussed above in section 5.1.1. The concentration range of TPhP detected in these products ranged from 0.88 to 62,000 ppm (Mendelsohn et al. 2016; Young et al. 2018; NIOSH 2019a; Tokumura et al. 2019; Estill et al. 2021; DTSC 2023b). Seventy-six nail product samples with TPhP detects from these studies are aggregated and graphed on a logarithmic scale (Figure 6).[39] As depicted in Figure 6, three distinct populations are present.

[39] *TPhP in different studies were reported in units of weight per weight (w/w) and weight per volume (w/v). In its recent study, DTSC found that of the various products that contain TPhP, the specific gravity ranged from 0.84 (a bitter additive to an anti-nail bite polish) to 1.1 g/ml (a nail polish/lacquer and a hard gel). Therefore, products reported in units of w/v when converted to ppm in units of w/w (and assuming a specific gravity of 1 g/ml) may be off by up to -16 to + 10%. Thus, the highest concentration found below the proposed AAT of 250 ppm (220 ppm w/v) could have been as high as 242 ppm w/w.*

- The first population has concentrations ranging from 0.88 to 220 ppm.
- The second population has concentrations ranging from 720 to 830 ppm.
- The third population has concentrations ranging from 2,550 to 62,000 ppm.

Based on Figure 6, DTSC anticipates that samples with concentrations closer to 0 ppm represent products with TPhP as a contaminant, while higher concentrations are representative of samples where TPhP is added as an intentional ingredient.

The data submitted in response to DTSC's information call-in supports DTSC's determination. Manufacturers reported TPhP in more than 1,100 nail products. Most of these products contained TPhP at concentrations of 5% (50,000 ppm) or less, aligning with the information in Figure 6. Additionally, TPhP was reported as a contaminant in 8.5% of nail product formulations in the concentration range of 0 to 0.1% (1000 ppm),[40] which includes the data points in the first population in Figure 6. Based on the groupings of the available data and call-in information from manufacturers, we estimate that TPhP concentrations below 250 ppm would represent a source of contamination in nail products.

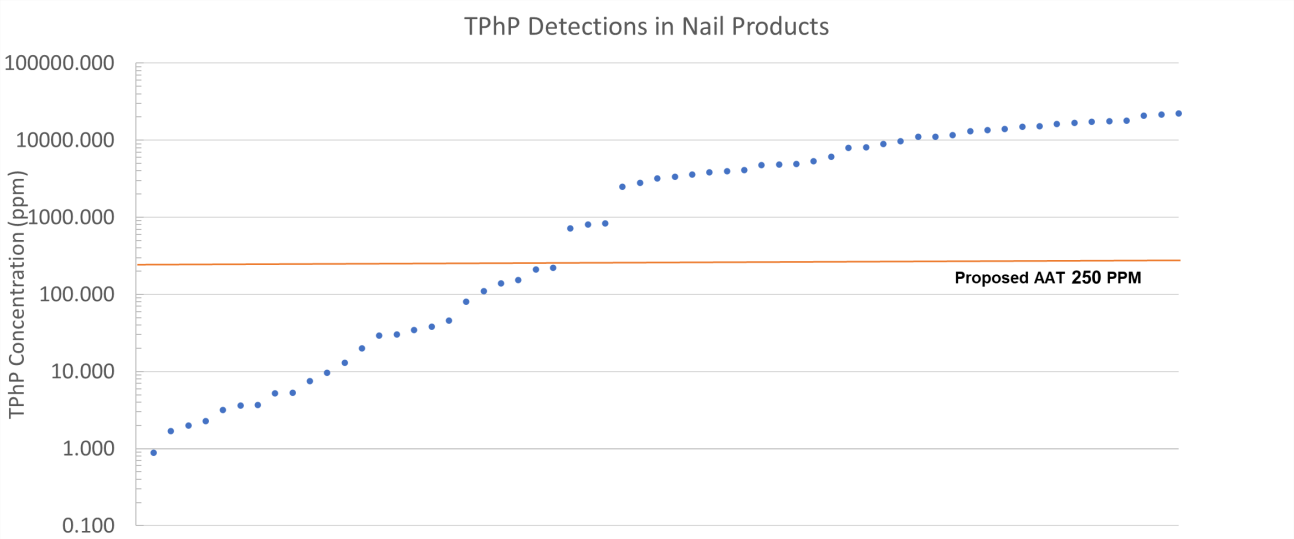


*Figure 6. TPhP detections in nail products from various studies. Detections (solid blue circles) are from DTSC analytical testing of nail products and data reported by Mendelsohn et al. (2016), Young et al. (2018), NIOSH (2019a), Tokumura et al. (2019), and Estill et al. (2021). The orange line is the proposed AAT of 250 ppm. The x-axis shows individual products.*

## Analytical Methods

[40] *The data call in did not provide concentrations for individual products. Responders only indicated whether the chemicals in their products fell within one of four predetermined ranges.*

Multiple approaches have been used to analyze TPhP in nail products, most of which indicate the ability to detect TPhP at concentrations at or below 250 ppm. DTSC relied on studies that reported TPhP concentrations at or below 250 ppm, summarized in Table 9, to inform its determination of acceptable analytical methods. While DTSC did conduct a study that detected TPhP in nail products (DTSC 2023b), the purpose of the study was to measure multiple ingredients. DTSC's analytical methods were not specifically optimized for TPhP, and thus the study is not included in Table 9. According to Table 9, the most common methods for detecting TPhP in nail products are high performance liquid chromatography coupled to mass spectrometry (HPLC/MS) and gas chromatography coupled to mass spectrometry (GC/MS). GC/MS is preferred for the quantitation of semi-volatile compounds in solid and aqueous samples, while HPLC/MS is suitable for the detection and quantitation of semi-volatile or nonvolatile compounds such as TPhP. MS provides the advantage of uniquely identifying a compound based on its retention time and the mass-to-charge ratios (m/z) of its fragment ions.

DTSC recommends using GC/MS, LC/MS, or non-determinative instruments such as gas chromatography coupled with flame photometric detector (GC/FPD) and gas chromatography coupled with flame ionization detector (GC/FID) to test for TPhP. Any other analytical technique that meets the method performance criteria described in the Requirements and Reporting section below may be used for sample preparation and measurement of TPhP concentrations in nail products.

*Table 9. TPhP Analytical Method Research Studies*

| Sample Material | Sample Preparation Procedure | Quantitation Procedure | Method Detection Limit (ppm) | References |
|---|---|---|---|---|
| Nail polish samples | Dissolved sample in methanol and extracted with methanol and acetone:ethyl acetate | Direct injection into HPLC-ESI MS/MS | 0.002 (LOD) | (Young et al. 2018) |
| Bulk samples containing nail polishes, base coats, and top coats | Dissolved in acetone | Direct injection into UPLC-APPI MS/MS | 0.10 (LOD) | (Estill et al. 2021) |

| Sample Material | Sample Preparation Procedure | Quantitation Procedure | Method Detection Limit (ppm) | References |
|---|---|---|---|---|
| Nail polish samples | Dissolved in acetone and diluted in dichloromethane | Direct injection into GC/EI-MS | NA | (Mendelsohn et al. 2016) |
| Nail polish samples | Dissolved in acetone and diluted in acetonitrile | Direct injection into HPLC-MS/MS in APCI mode | 0.34 (reporting limit) | (Tokumura et al. 2019) |
| Bulk nail polish samples | Dissolved in acetone | Injection into GC with a flame photometric detector (GC/FPD) | 0.3 (LOD) | (NIOSH 2019a) |

*HPLC-ESI MS/MS = High performance liquid chromatography coupled to electrospray triple quadropole mass spectrometry.*
*UPLC-APPI MS/MS = Ultraperformance liquid chromatography coupled to atmospheric pressure photoionization triple quadropole mass spectrometry.*
*GC/EI-MS = Gas chromatography coupled to electron impact single quadropole mass spectrometry.*
*HPLC-MS/MS in APCI mode = High performance liquid chromatography coupled to triple quadropole mass spectrometry in atmospheric pressure chemical ionization mode.*
*GC/FPD = Gas chromatography with flame ionization detection*

## Requirements and Reporting

When a manufacturer submits an AAT Notification instead of an Alternatives Analysis Report, it must demonstrate and certify that the concentration of TPhP in the product does not exceed the AAT. To establish compliance with the AAT exemption, a manufacturer may either measure the TPhP concentration in each Priority Product and submit the corresponding laboratory testing results or obtain certificates from the ingredient suppliers. The certificates should pertain to ingredients known or suspected to contain TPhP and should specify the TPhP concentration in the source materials used to manufacture each Priority Product. When a manufacturer provides information obtained from the ingredient suppliers, the manufacturer must also submit calculations of the final concentration of TPhP for each formulated Priority Product.

When submitting laboratory testing results, manufacturers must provide the analytical data, the laboratory testing methodology, and the quality control and assurance protocols followed to measure TPhP in the Priority Product, as well as the name and location of the testing laboratory that conducted the analysis. A manufacturer can assert a claim of Trade Secret Information. The information submitted

for compliance certification can be submitted through DTSC's CalSAFER website, which is equipped to receive and securely handle such information.

In addition, each AAT Notification must also include a demonstration that the manufacturer will continue to meet the AAT. If, at any point, the concentration of TPhP in the Priority Product no longer falls at or below the AAT, the manufacturer is required to notify DTSC within 30 days of the change and must submit a Preliminary AA Report or a Chemical or Product Replacement or Removal Notification within 180 days of the change.

Every testing laboratory that conducts the analysis a manufacturer uses to certify that the concentration of TPhP in a nail product does not exceed the AAT, must meet the method performance criteria described below. The method performance criteria are comprised of the sample preparation criteria, analytical method criteria, instrument criteria, calibration criteria, sample analysis criteria, and quality control criteria. The method performance criteria described below are relevant to GC/MS/MS based analysis. If another instrument platform (i.e., LC/MS/MS) is used, similar criteria and recommendations, as outlined in the Calibration Criteria and Sample Analysis Criteria sections below, must be established and defined in the methodology. For non-determinative instruments (i.e., GC/FPD and GC/FID), dual column confirmation of TPhP is required. Any analytical method that meets the method performance criteria may be used for sample analysis and determination of triphenyl phosphate concentrations in nail products.

### Sample Preparation Criteria

1. Each nail product shall be gently mixed or shaken prior to taking an aliquot of the product to ensure the aliquot is representative of the contents in the container.
2. Each aliquot of nail product shall be measured in units of mass (example, milligram, gram, etc.) for the analysis.
3. A sample may be extracted by various techniques including, but not limited to shaking, sonicating, and/or vortexing and may be introduced into the analytical instrument by direct injection, provided that all other performance criteria are met.
4. A surrogate shall be required; all samples must be spiked with the appropriate surrogate.

### Analytical Method Criteria

1. An internal standard shall be added to each sample, prior to introduction into the analytical instrument, at a concentration within the calibration range for triphenyl phosphate.
2. A signal-to-noise ratio of 3:1 or greater shall be met for all quantitation and qualifier ions for triphenyl phosphate in all samples.
3. The limit of quantitation for triphenyl phosphate shall be 100 ppm or less.

## Instrument Criteria

1. All study samples shall be analyzed on a properly tuned instrument that meets the instrument manufacturer's specifications (i.e., mass spectrometer tune, mass calibration check, or qualitative identification criteria). If the instrument requirements are outside the acceptable criteria, standard measures to correct the problem shall be implemented prior to analyzing samples.

## Calibration Criteria

1. The instrument tune checks shall be done prior to calibration.
2. Retention time for calibration standards:
    a) After the initial calibration, the retention time of each internal standard in the sample shall be within ±30 seconds (0.5 min) of the retention time of the internal standard at the midpoint of the initial calibration; and
    b) The relative retention time of the analyte of interest shall be within ±30 seconds (0.5 min) compared to the midpoint of the initial calibration or continuing calibration verification standard for all calibration standards.
3. The fitted line of the initial calibration shall consist of a minimum of five non-zero calibration concentrations. The concentration of the analyte in the lowest standard solution shall be accurate within 50 percent of its true concentration value, and all other calibration levels must be within 30 percent of their true value. The fitted line of the initial calibration shall meet one of these two criteria:
    a) The relative standard deviation, expressed as a percentage, shall not exceed 20 percent. This is the ratio of the standard deviation to the mean of the response factor for triphenyl phosphate; or
    b) The linear fit shall have a correlation coefficient greater than 0.99.
4. An initial calibration verification standard solution, with a concentration at or near the mid-point of the calibration curve, shall be analyzed immediately following the initial calibration, and the calculated concentration of triphenyl phosphate shall be within 30 percent of its true concentration value. No samples shall be run until the initial calibration verification standard solution is analyzed and the criteria met.
5. A continuing calibration verification standard solution shall be analyzed before sample analysis, after every ten samples, and at the end of the analysis sequence. The measured concentration of the continuing calibration verification standard solution shall be within 20 percent of its true concentration value. If the calibration verification does not meet the acceptance criteria, standard measures to correct the problem shall be implemented. If the response of the continuing calibration verification standard solution is still not within 20 percent of its true concentration value, a new initial calibration shall be conducted.

6. The internal standard responses in the calibration standards, the initial verification calibration standard, and the continuing calibration verification standards shall be 50-200% of the response of the internal standard of the mid-point of the calibration curve.

### Sample Analysis Criteria

1. The retention time of the target analyte in the samples shall be within ±30 seconds (0.5 min) of the retention time of either the mid-point concentration standard solution of the initial calibration or the preceding continuing calibration verification standard solution of the analytical sequence.
2. The internal standard responses in the samples shall be 50-200% of the response of either the mid-point concentration standard solution of the initial calibration or the preceding continuing calibration verification standard.

### Quality Control Criteria

1. All data shall adhere to a quality control protocol that includes, for each batch of 20 samples, for each type of nail product analyzed:
    a) Preparation and analysis of a method blank.
    b) Preparation and analysis of a duplicate sample.
    c) Preparation and analysis of a matrix spike and matrix spike duplicate.
    d) Preparation and analysis of a laboratory control sample and laboratory sample duplicate.
2. Each product sample, method blank, duplicate sample, matrix spike, matrix spike duplicate, laboratory control sample, and laboratory control sample duplicate shall be spiked with a surrogate standard solution prior to extraction and analysis. The recommended criteria are outlined below. Alternate requirements are acceptable as long as they meet analytical accuracy and precision for the batch of samples.
3. Insert a sufficient number of solvent blanks between samples to verify no carryover or cross contamination of triphenyl phosphate from one sample to the next.
4. The measured concentration of the surrogate standard solution in each product sample, method blank, duplicate sample, matrix spike, matrix spike duplicate, laboratory control sample, and laboratory control sample duplicate undergoing analysis shall be within 70 to 130 percent of the spiked concentration.
5. The concentration of triphenyl phosphate in each method blank shall not exceed one half of the limit of quantitation.
6. The laboratory control sample and laboratory control sample duplicate shall be analyzed and be accurate within 30 percent of their true concentration value and precise, with a relative percent difference less than or equal to 20 percent.

7. The matrix spike and matrix spike duplicate shall be between 70 and 130 percent of the spiked concentration, and a relative percent difference shall be less than or equal to 20 percent.

## Definitions

Partially adapted from Chapter One of the SW-846 Compendium for Hazardous Waste Test Methods (U.S. EPA 2014).

"Aliquot" is a measured portion of a total amount of a larger sample solution or suspension.

"Continuing Calibration Verification (CCV) Standard" is a mid-range concentration standard analyzed before, during, and at the end of an analytical batch and verifies that the instrument response has not drifted from the initial calibration response. This standard solution contains a known concentration of the target analyte and is typically derived from the same source as the initial calibration standards.

"Correlation coefficient ($r^2$)" is a statistical measure of the strength of the relationship between two variables.

"Initial Calibration (ICAL)" is a determination of the instrument response over a range of known concentrations of an analyte or analytes. A series of standard solutions is prepared from a certified reference material and analyzed on the instrument prior to any samples. Five or more standard solutions containing progressively higher concentrations of the analytes of interest are generally prepared.

"Initial Calibration Verification (ICV) Standard" is a certified solution from a source other than that used for the initial calibration standards and is used to verify the accuracy of the initial calibration.

"Internal Standard (IS)" is a chemical substance that is similar, but not identical, to the target analyte and is added to each sample at a known concentration. The internal standard mimics the behavior of the target analyte but has a different signal than the analyte. An internal standard is used for quantitation of target analytes and to account for matrix effects and/or variability in instrument response by normalizing the response of the target analytes and surrogates, thereby decreasing measurement bias.

"Laboratory Control Sample/Laboratory Control Sample Duplicate (LCS/LCSD)" is a clean matrix or an extraction solvent that has been spiked with a known concentration of the target analyte. It is prepared and analyzed in the same analytical batch and in exactly the same manner as the other samples. The laboratory control sample and laboratory control sample duplicate are used to assess general method performance based on the ability of the laboratory to successfully recover target analytes.

“Matrix Spike/Matrix Spike Duplicate (MS/MSD)” are quality control samples that contain known concentrations of target analytes that have been added to one of the batch nail product samples before extraction and analysis.

“Method Blank” is a clean matrix or an extraction solvent. It is used to assess background interference or contamination in the analytical system that might lead to reporting of elevated concentration levels or false positive data.

“Percent Recovery” is the proportion of the concentration of a target analyte measured in a sample relative to the known concentration spiked into a sample, conveyed as a percentage.

“Quantitation limit (QL)” is the lowest calibration concentration multiplied by the dilution factor.

“Relative Percent Difference (RPD)” is the absolute difference between two measurements, divided by their average, converted to percentage.

“Relative Standard Deviation (RSD)” is the standard deviation of a group of measurements in a data set, divided by their average, converted to percentage. Relative standard deviation is an indicator of how a group of measurements in a data set are scattered around the mean.

“Response Factor (RF)” is the ratio between a signal produced by an analyte and the concentration of analyte that produced the signal.

“Signal-to-Noise Ratio (S/N)” is the ratio of a desired signal (i.e., the change in instrument response to the presence of a substance) to the level of background noise (i.e., the fluctuation in the instrument background signal).

“Surrogate” is the compound that is used to monitor extraction and analysis efficiency of the method.