Technical Document for the Proposal to Add para-Phenylenediamine Derivatives to the Candidate Chemicals List

SEPTEMBER 2023

Prepared by

DEPARTMENT OF TOXIC SUBSTANCES CONTROL

SAFER CONSUMER PRODUCTS PROGRAM

California Environmental Protection Agency

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Derivatives of *para*-Phenylenediamine (p-phenylenediamine, or PPD) have recently raised significant global concern after a transformation product of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was identified as the cause of mass die-offs of coho salmon (*Oncorhynchus kisutch*) (Tian et al. 2021; Tian et al. 2022). Since then, the global community has become increasingly aware of the widespread presence of 6PPD and other PPD derivatives in consumer products and the environment (Cao et al. 2022; Zhang et al. 2022; Wang et al. 2022; Johannessen and Metcalfe 2022).

The high reactivity of PPD and its derivatives makes these chemicals useful in a variety of industrial applications. For example, because PPD reacts readily with oxygen, it is used as a hair dye and henna substitute, an antioxidant in rubber and gasoline, and in photographic processing (PubChem 2022). 6PPD is used as an antiozonant, antioxidant, and free-radical scavenger in rubber products, including motor vehicle tires (DTSC 2022). Other PPD derivatives are similarly used in rubber products (Zhao et al. 2023).

As a result of their widespread use in consumer products, various PPD derivatives have been detected in aquatic environments (Tian et al. 2021; Johannessen et al. 2021a; Klöckner et al. 2021; Cao et al. 2022), wastewater effluent (Johannessen and Metcalfe 2022), air (Cao et al. 2022; Zhang et al. 2022; Wang et al. 2022; Johannessen et al. 2022), as well as soil and dust (Huang et al. 2021; Liang et al. 2022; Deng et al. 2022). The PPD derivatives studied to date are potent aquatic toxicants or skin sensitizers, which indicates a potential for adverse impacts to human and ecological health from exposures to members of this chemical class. Sensitive subpopulations such as workers, as well as aquatic ecosystems and threatened and endangered species, may be especially vulnerable to these impacts. Based on these findings, we propose adding this class of chemicals, as defined below, to the Department of Toxic Substances Control (DTSC)'s Candidate Chemicals List.

This document explains the rationale for this proposal. Listing a chemical or chemical class as a Candidate Chemical does not place regulatory obligations on chemical manufacturers or on product manufacturers that use the chemical. However, it does give DTSC the option of regulating the chemical or class in specific consumer products in the future, based on certain findings. Under the Safer Consumer Product Regulations, DTSC may list a consumer product containing one or more Candidate Chemicals as a Priority Product if it finds evidence for potential exposures to the Candidate Chemical(s) in the product and potential significant or widespread adverse impacts from those exposures. Priority Product manufacturers have several options for complying with such a regulation, including evaluating whether there are safer alternatives to the Chemical(s) of Concern in their product.

DTSC finalized regulations listing motor vehicle tires containing 6PPD as a Priority Product. Adding these tires to DTSC's Priority Product List will compel tire manufacturers to identify and evaluate

potential alternatives to 6PPD that ensure tire safety and performance while also preventing harm to salmon and other aquatic species. PPD derivatives may be potential alternatives to 6PPD. Adding this entire chemical class to the Candidate Chemicals List will help ensure that manufacturers fully evaluate the tradeoffs if they propose switching from 6PPD to another PPD derivative.

2.   CHEMICAL DEFINITION

This chemical class comprises *para*-phenylenediamine (also known as PPD, benzene-1,4-diamine [IUPAC[1]], 1,4-diaminobenzene, and 1,4-phenylenediamine) (Figure 1) and all its derivatives that:

- Have one or two substituents[2] on one or both PPD nitrogen atoms (Figure 1b);
- Contain no additional substituents or modifications to the PPD phenyl ring at the 2, 3, 5, or 6 positions (Appendix A, Figure 1);
- Substitute any hydrogen in the PPD amine groups with nitrogen or carbon only;
- Do not contain nitrogen-nitrogen double bonds or nitrogen-nitrogen triple bonds at either PPD nitrogen atom;
- Contain no quaternary amines[3] (i.e., quaternary ammonium cations) anywhere in the molecule; and
- Have a molecular weight of 1000 daltons (Da) or less (for reference, the molecular weight of 6PPD is 268 Da). In multicomponent compounds[4], this applies only to those components[5] that are PPD derivatives, as defined above.

---

[1] *International Union of Pure and Applied Chemistry*

[2] *A substituent is an atom or group of atoms other than hydrogen attached to a carbon atom in a molecule (i.e., the missing hydrogen was substituted with that atom or group) (UCLA 2023).*

[3] *Quaternary amines (i.e., quaternary ammonium cations) are part of quaternary ammonium compounds, i.e., derivatives of ammonium compounds, $(NH_4^+)Y^-$, in which all four of the hydrogens bonded to nitrogen have been replaced with hydrocarbyl groups (IUPAC 2014).*

[4] *A multicomponent compound is a mixture of two or more distinct chemicals (for example, 1,4-benzenediamine, ethanedioate (1:1), CASRN 62654-17-5). Such compounds may also be called multi-constituent substances.*

[5] *A component is a constituent of a mixture whose amount or concentration can be varied independently (IUPAC 1996).*

The *para*-phenylenediamine derivatives (PPD derivatives) class includes any chemical that contains a component with the above properties.
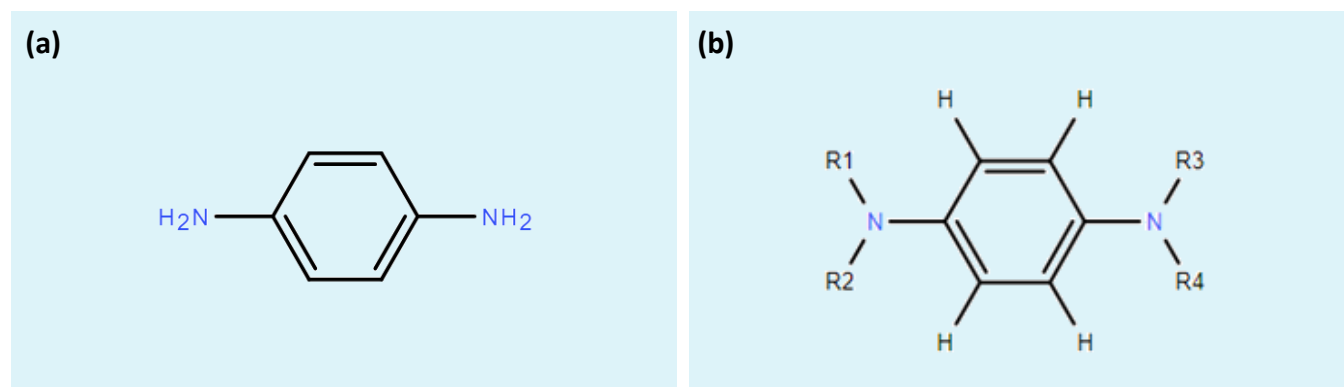

Figure 1. (a): para-Phenylenediamine (PPD) (CASRN 106-50-3) (PubChem 2022). (b): PPD moiety and R groups that form PPD derivatives. The two PPD nitrogen atoms can be bound only to carbon or nitrogen atoms in R groups. The N–R bonds cannot be nitrogen-nitrogen double or triple bonds.

This definition aims to ensure that the chemical class primarily captures highly reactive molecules. We integrated research on known PPD derivatives (Table 1) with resonance theory to define a chemical class expected to be highly toxic and representative of the more-studied PPD derivatives. PPD, the parent molecule whose structure forms the basis for this chemical class, is well known to display high reactivity and act as a skin sensitizer (McFadden et al. 2007; Chipinda et al. 2011; Meyer and Fischer 2015). Stahl et al. (1990) found greater aquatic toxicity in the *para* isomer compared to the *meta* and *ortho* isomers[6] in all trophic levels (Appendix B, Table 1).

This definition focuses on substituent characteristics that increase the reactivity of the phenyl ring. Substituents affect a phenyl ring's affinity for electrophilic (i.e., electron-loving) aromatic substitution (Hunt 2023). In general, substituents with relatively high electronegativity (e.g., nitro groups) withdraw electron density from phenyl rings and consequently function as deactivating groups, while substituents with relativity low electronegativity (e.g., amino groups) are electron-donating (or activating) groups (Hunt 2023). The PPD derivatives class also excludes molecules in which either PPD nitrogen shares a double (i.e., azo) or triple bond with another nitrogen or is bound to an atom other

---

[6] *Two phenyl ring substituents are* ortho *if they occupy adjacent positions (positions 1 and 2). They are* meta *if they are separated by one ring carbon (positions 1 and 3). They are* para *if they are separated by two ring carbons (positions 1 and 4—in which case they occupy opposite sides of the ring). See Appendix A, Figure 1.*

than carbon or nitrogen (such as in nitroso groups). Azo bonds are expected to reduce phenyl ring reactivity by withdrawing electrons (Kyziol and Frej 1988), and many azo dyes are already on DTSC's Candidate Chemicals List (DTSC 2023). Nitrogen atoms on PPD moieties are positively charged when triply bound to another nitrogen and should therefore deactivate the phenyl ring to electrophilic attack, as discussed above. We also exclude quaternary ammonium compounds (QACs) because the entire class of QACs is already present on DTSC's Candidate Chemicals List (DTSC 2023).

Additionally, we excluded PPD derivatives with additional substituents on the phenyl ring because formation of transformation products such as quinones involves oxidation of the phenyl ring, and replacing the hydrogens bound to phenyl ring carbons 2, 3, 5, or 6[7] would potentially block such transformations. The more-studied members of this class that demonstrate the greatest toxicity contain no substituents on the PPD phenyl ring other than the two PPD nitrogens.

Finally, we set an upper limit of 1,000 Da on the molecular weight because molecules above that threshold show limited absorption by cells (Mayo-Bean et al. 2017) and, consequently, limited dermatotoxicity or acute aquatic toxicity. Evidence suggests that some PPD derivatives act as haptens to provoke allergic sensitization and dermatotoxicity (Venkatesan et al. 2021). Haptens that provoke allergic reactions in the skin are described as molecules smaller than 1,000 Da (Chipinda et al. 2011). While developing models for acute aquatic toxicity, the U.S. Environmental Protection Agency (U.S. EPA) (Mayo-Bean et al. 2017) wrote:

> Molecular weight may also be considered to determine the absorption cutoff limit for aquatic organisms. As the molecular weight of a chemical increases above 600, passive absorption through respiratory membranes decreases significantly. Therefore, for chemicals with molecular weights > 1,000 Da, it has been assumed that such absorption is negligible (Mayo-Bean et al. 2017).

By restricting molecular weight to 1,000 Da, our definition focuses on chemical entities with greater potential to pass through membranes and be absorbed by target organisms.

---

[7] *Chemists typically number the carbon atoms in a six-carbon phenyl ring one through six. Determining which carbon is designated one (1) is not always trivial, but the carbons are always numbered consecutively. In the PPD molecule, the -NH₂ substituents occupy the 1 and 4 (*para*) positions, and the carbons in positions 2, 3, 5, and 6 are bound to hydrogen atoms (*Appendix A, Figure 1*).*

PPD Derivative Identification

To explore the chemicals in this class, we used U.S. EPA's Hazard Comparison Dashboard (HCD) (U.S. EPA 2023a). The HCD is a web-based tool for identifying chemicals with related structures and their associated traits, such as experimental and predicted physicochemical properties, environmental fate and transport information, and available toxicity data (U.S. EPA 2023a). Quantitative structure-activity relationship (QSAR) predictive tools, such as U.S. EPA's Toxicity Estimation Software Tool (TEST)[8] and the Open (Quantitative) Structure-activity/property Relationship App (OPERA), are incorporated into the HCD *Hazard* module to fill data gaps for some toxicity endpoints. We generated a list of 1,849 compounds by running a substructure search of the HCD, using PPD as the base structure, and applying the constraints listed in our class definition with further refinement in the HCD's *ToxPrints* module to remove QACs (U.S. EPA 2023a).
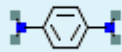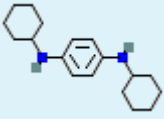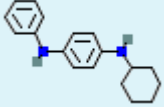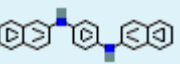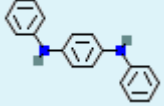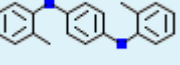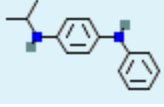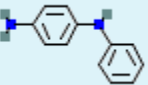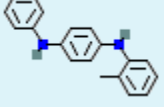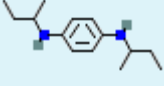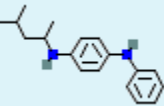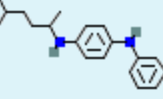
The 1,849 chemicals identified as members of the PPD derivatives class are all present in U.S. EPA's CompTox and Distributed Structure-Searchable Toxicity (DSSTox) Databases (U.S. EPA 2023b; U.S. EPA 2023c). Chemicals in DSSTox are compiled from public sources, such as the National Institutes of Health (NIH) PubChem database, with differing levels of reliability and accuracy (U.S. EPA 2023b). Data entries in the CompTox and DSSTox databases range from high-confidence expert curation to low-confidence programmatic curation (Appendix A, Table 1). Approximately 3.9% of the 1,849 PPD derivatives are expertly curated (QC 1 and 2); the rest are programmatically curated.

In general, PPD derivatives are a poorly characterized class of chemicals. Here, we define a chemical class based on a chemical moiety (i.e., the PPD structure) and structural similarity with certain members of the class with known hazard traits. Table 1 presents a subset of the class of PPD derivatives that are referred to throughout this document as the "more-studied" PPD derivatives and are associated with referenced research, including experimental data and modeled information, to support adding the class of PPD derivatives to the Candidate Chemicals List. The distinction between "more-studied" PPD derivatives in Table 1 and "less-studied" PPD derivatives that describe the rest of the class is unique to this document.

---
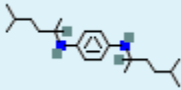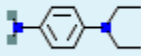
[8] *U.S. EPA's TEST is available as a downloadable software tool and as part of a Java-based web service called Web-services Toxicity Estimation Software Tool (WebTEST). While the hazard modeling for this document was completed using the WebTEST user interface within the HCD, both are referred to as "TEST" in this document.*

Table 1: PPD and the "more-studied" PPD derivatives referenced in this document. CASRNs, names, and structures provided by PubChem (PubChem 2023).

PPD Derivative (CASRN)	Unabbreviated Name	IUPAC Name	Structure
PPD (106-50-3)	p-Phenylenediamine	Benzene-1,4-diamine	
CCPD (4175-38-6)	N,N'-Dicyclohexyl-p-phenylenediamine	1-N,4-N-dicyclohexylbenzene-1,4-diamine	
CPPD (101-87-1)	N-Cyclohexyl-N'-phenyl-p-phenylenediamine	1-N-cyclohexyl-4-N-phenylbenzene-1,4-diamine	
DNPD (93-46-9)	N,N'-Di-2-naphthyl-p-phenylenediamine	1-N,4-N-dinaphthalen-2-ylbenzene-1,4-diamine	
DPPD (74-31-7)	N,N'-Diphenyl-p-phenylenediamine	1-N,4-N-diphenylbenzene-1,4-diamine	
DTPD (27417-40-9)	N,N'-Ditolyl-p-phenylenediamine	1-N-(2-Methylphenyl)-4-N-(4-methylphenyl)benzene-1,4-diamine	
IPPD (101-72-4)	N-Isopropyl-N'-phenyl-p-phenylenediamine	1-N-phenyl-4-N-propan-2-ylbenzene-1,4-diamine	
PPPD (101-54-2)	N-Phenyl-p-phenylenediamine	4-N-phenylbenzene-1,4-diamine	
PTPD (27173-16-6)	N-Phenyl-N'-(o-tolyl)-p-phenylenediamine	4-N-(2-methylphenyl)-1-N-phenylbenzene-1,4-diamine	
44PD (101-96-2)	N,N'-Di-sec-butyl-p-phenylenediamine	1-N,4-N-di(butan-2-yl)benzene-1,4-diamine	
6PPD (793-24-8)	N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine	4-N-(4-methylpentan-2-yl)-1-N-phenylbenzene-1,4-diamine	
7PPD (3081-01-4)	N-(1,4-Dimethylpentyl)-N'-phenyl-p-phenylenediamine	4-N-(5-methylhexan-2-yl)-1-N-phenylbenzene-1,4-diamine	

PPD Derivative (CASRN)	Unabbreviated Name	IUPAC Name	Structure
77PD (3081-14-9)	N,N'-Bis(1,4-dimethylpentyl)-p-phenylenediamine	1-N,4-N-bis(5-methylhexan-2-yl)benzene-1,4-diamine	
N,N-Diethyl-PPD (93-05-0)	N,N-Diethyl-p-phenylenediamine	4-N,4-N-diethylbenzene-1,4-diamine	

3. POTENTIAL FOR ADVERSE IMPACTS

3.1. Hazard Traits, Toxicological and Environmental Endpoints That are the Basis for This Listing

Reference: California Code of Regulations, Title 22, sections 69502.2(b)(1)

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 Green Chemistry Hazard Trait Regulations (California Code of Regulations, Title 22, Chapter 54). These include exposure potential, and toxicological and environmental hazard traits.

PPD derivatives, based on current evidence, can reasonably be expected to have one or both of the following hazard traits:

- Dermatotoxicity
- Wildlife Survival Impairment

PPD derivatives are largely defined by the structural similarities within the class. Section 69502.2(b)(1)(D) of the California Code of Regulations (CCR) provides the basis to extrapolate from well-characterized members of the class to the less-studied members in order to model the hazard traits.

We used the HCD's *Hazard* module to produce screening hazard estimates for the 1,849 PPD derivatives described above. The HCD compiles chemical hazard data from multiple publicly available sites, databases, and sources, including U.S. federal and state sources and international bodies (Vegosen and Martin 2020). The HCD adopts a modified version of the GreenScreen® method, which classifies data sources as authoritative or screening sources. Authoritative sources have a higher level of confidence because they are "generated by recognized experts, often as part of a government regulatory process to identify chemicals and known associated hazards" (Clean Production Action

2018; Vegosen and Martin 2020). Predictive source lists are from QSAR model estimates are integrated into the HCD to fill data gaps (Vegosen and Martin 2020). A single hazard score for each endpoint of concern is based on a trumping scheme where the most conservative value (very high [vH] > high [H] > medium [M] > low [L]) from the most authoritative source determines the final score (Vegosen and Martin 2020). Hazard endpoint definitions and score criteria are based mostly on the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (Vegosen and Martin 2020). The hazard scores provided are estimates and should not be regarded as final hazard determinations (Vegosen and Martin 2020). The distribution of PPD derivatives' hazard scores generated by the HCD are shown in Table 2. Seventy-four chemicals, or 4% of the 1,849, were scored for skin sensitization, and all 74 were classified as *high* hazard. The percentage of PPD derivatives with a hazard score in HCD was better for acute aquatic toxicity than skin sensitization. 1,705 chemicals, about 92%, produced a hazard score using the HCD. The majority had *high* or *very high* acute aquatic toxicity (Table 2). A more thorough discussion of these hazard traits follows, with specific examples from the class.

Table 2: Summary hazard score outputs from the HCD for the 1,849 PPD derivatives identified. These scores are based on empirical or modeled data. Only chemicals with hazard score determinations are shown; PPD derivatives that did not receive scores are not included (U.S. EPA 2023a).

Hazard Endpoint	Description	L	M	H	vH	Total
Skin Sensitization	n	0	0	74	N/A	74
	% of scores	0%	0%	100%	N/A	100%
Acute Aquatic Toxicity	n	196	293	501	715	1,705
	% of scores	11%	17%	29%	42%	100%

Key: L = low; M = medium; H = high; vH = very high. vH not applicable (N/A) for skin sensitization because the category is not included in GHS. n = number of chemicals.

Evidence for Dermatotoxicity

Reference: California Code of Regulations, Title 22, section 69403.2

Toxicological endpoints for dermatotoxicity include but are not limited to those indicating allergic sensitization and allergic reactions, among others, measured in in vivo or in vitro skin models. Relevant data for this hazard endpoint include in vitro *measures of dermatotoxicity, such as toxicity in cell-based models, and structural or mechanistic similarity to other chemical substances that are dermatotoxic.*

PPD

para-Phenylenediamine (PPD) is the parent structure of this class and is recognized by the U.S. Consumer Product Safety Commission (CPSC) as a strong sensitizer (16 CFR 1500.13). The U.S. Food and Drug Administration (FDA) lists PPD as a common allergen found in cosmetics (U.S. FDA 2022a). In a fact sheet on black henna, it describes PPD as capable of causing "dangerous skin reactions in some

people" (U.S. FDA 2022b), and PPD is not permitted in cosmetics intended to be applied to the skin (U.S. FDA 2022b). The European Chemicals Agency (ECHA) recognizes PPD as a skin sensitizer (ECHA 2022). Under ECHA, PPD bears the GHS hazard phrase, "H317: May cause an allergic skin reaction" (NIH 2021; ECHA 2022).

U.S. EPA includes PPD as a hazardous air pollutant (HAP) under the Clean Air Act (U.S. EPA 2015a). Chemicals listed as HAPs have been adopted by California as toxic air contaminants (TAC) (CARB 1993); this is the reason for PPD's presence on the Candidate Chemicals List (DTSC 2023). U.S. EPA's Health Effects Notebook for PPD states that it may cause severe dermatitis (U.S. EPA 2000). Chronic exposures to PPD may result in eczematoid contact dermatitis (U.S. EPA 2000). Short-term exposures to high levels of PPD may also result in gastritis, renal failure, vertigo, convulsions, and coma in humans (U.S. EPA 2000). Human and animal studies have confirmed the sensitizing properties of PPD (McFadden et al. 2007; Aeby et al. 2009). A workshop on allergic contact dermatitis, convened by the German Federal Institute for Risk Assessment (BfR), states that the "allergic reactions caused by hair dye ingredients (e.g., PPD) are of special concern because of their severity and widespread use" (Peiser et al. 2012). This concern is exacerbated by the possibility of cross-reactivity among other chemicals in the class, such as IPPD (Peiser et al. 2012). McFadden et al. (2007) refer to PPD as "among the most potent" contact allergens.

Mechanism

The reactivity of PPD is the underlying reason for its action as a sensitizer (McFadden et al. 2007; Chipinda et al. 2011; Meyer and Fischer 2015). Some small, reactive molecules like PPD act as haptens, which are chemicals that bind to proteins in the body and can provoke an immune response (NCBI 1965; Chipinda et al. 2011). Many researchers have studied PPD's potential to cause allergic contact dermatitis because of its prevalence in permanent hair dye and henna tattoo inks and the resulting allergic contact dermatitis. This body of work provides a good understanding of PPD's action as a sensitizer (Aeby et al. 2009; Chipinda et al. 2011; Meyer and Fischer 2015). PPD is broadly recognized as a pre- or prohapten, which, upon oxidation (either by oxygen in air or metabolically within the skin), can transform into haptens (Meyer and Fischer 2015). PPD's oxidation products include benzoquinone diamine, benzoquinone, and Bandrowski's Base (a trimer of PPD) (Meyer and Fischer 2015). The haptens are reactive electrophiles that bind to proteins at amino acid residues such as cysteine (Aeby et al. 2009; Jenkinson et al. 2010; Chipinda et al. 2011; Meyer and Fischer 2015). For example, Jenkinson et al. (2010) demonstrated that PPD itself, as well as its oxidized products, bonds to albumin (Jenkinson et al. 2010), the most abundant circulating protein in blood plasma (Moman et al. 2023). Hapten-protein complexes may induce an immune response and result in sensitization (Basketter et al. 2008). Subsequent skin contact with the hapten-protein complex will elicit a reaction called allergic contact dermatitis (Basketter et al. 2008).

Other PPD Derivatives are Skin Sensitizers

All 74 PPD derivatives with skin sensitization information in the HCD received a *high* hazard score (Table 2). 86% of these hazard scores (64 of 74) for PPD derivatives are solely based on QSAR estimates from the Ministry of Environment and Food of Denmark. Denmark used QSAR models to predict GHS hazard categories for the Advisory List for Self-Classification of Dangerous Substances (Vegosen and Martin 2020). 14% of the hazard scores for skin sensitization (10 of 74) for PPD derivatives are based on authoritative or screening sources (Table 3). These sources include ECHA's Classification Labeling and Packaging (CLP) Annex VI, Japan's National Institute of Technology and Evaluation (NITE) Classification Results, and Germany's Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission). Some PPD derivatives in our class have *high* hazard scores for skin sensitization based on HCD-designated authoritative, screening, and predictive sources from international agencies that regulate chemicals.

Table 3: Ten PPD derivatives with high hazard scores based on authoritative or screening sources.

PPD Derivative (CASRN)	Reference	Source Type
PPD (106-50-3)	ECHA CLP[a] Germany[b]	Authoritative Authoritative
CPPD (101-87-1)	Germany[b]	Authoritative
DPPD (74-31-7)	ECHA CLP[a] Germany[b]	Authoritative Authoritative
IPPD (101-72-4)	ECHA CLP[a] Germany[b]	Authoritative Authoritative
PPPD (101-54-2)	Germany[b]	Authoritative
6PPD (793-24-8)	Germany[b]	Authoritative
1,3,5-Triazine-2,4,6-triamine, N2,N4,N6-tris[4-[(1,4-dimethylpentyl)amino]phenyl]- (121246-28-4)	ECHA CLP[a]	Authoritative
Benzenesulfonic acid, 2-[(4-aminophenyl)amino]-5-nitro- (91-29-2)	Germany[b]	Authoritative
N-(1-Methylheptyl)-N'-phenyl-1,4-benzenediamine (15233-47-3)	Australia[c]	Screening
N,N-Diethyl-PPD (93-05-0)	Japan[d]	Screening

[a] = ECHA 2023a   [b] = Deutsche Forschungsgemeinschaft 2017
[c] = Safe Work Australia 2023   [d] = NITE 2023

Conclusion

All the PPD derivatives with information in HCD have a *high* skin sensitization hazard score (Table 2). The *high* hazard categorization comes from agencies from around the world that regulate chemicals, meeting DTSC's criteria as reliable information. Several of the PPD derivatives can act as haptens, which can provoke allergic sensitization, in part because of their chemical reactivity (Chipinda et al. 2011; Peiser et al. 2012). Other PPD derivatives are reasonably expected to be skin sensitizers and cause dermatotoxicity because of their shared structure and attributes. The potential for dermatotoxicity merits the inclusion of PPD derivatives on DTSC's Candidate Chemicals List.

Evidence for Wildlife Survival Impairment

Reference: California Code of Regulations, Title 22, section 69404.9

Environmental endpoints for wildlife survival impairment include but are not limited to those indicating death, aquatic toxicity, behavioral impacts, increased disease susceptibility, and changes in population viability. Relevant data for this hazard trait include in vitro measures of ecotoxicological endpoints and structural or mechanistic similarity to other chemical substances shown to impair wildlife survival.

Based on the HCD's *Hazard* module outputs, 71% of the 1,849 identified chemicals in the PPD derivatives class have *high* or *very high* hazard scores for acute aquatic toxicity. This section first focuses on *in vivo* data demonstrating aquatic toxicity of the more-studied members of the PPD derivatives class. In the latter part of this section, we discuss the modeled evidence suggesting that structurally similar chemicals impair wildlife survival. Collectively, these sections provide evidence for inclusion of PPD derivatives on DTSC's Candidate Chemicals List.

Authoritative and Empirical Data

The more-studied PPD derivatives are frequently categorized as having *very high* aquatic toxicity across all trophic levels of the aquatic food chain, based on GHS criteria (Table 4) (ECHA 2020a). Table 4 shows several of the more-studied PPDs and the relevant aquatic toxicity information from chemical registration data in the 77PD dossier that was submitted to ECHA, with additional information, as referenced. Toxicity values from dossiers were accepted as reliable information pursuant to section 69501.1(a)(57)(A)(3). More detailed information on the toxicity of the more-studied PPD derivatives can be found in Appendix B.

Table 4: Aquatic toxicity values from ECHA dossiers and other sources. The table is adapted from the 77PD dossier (ECHA 2020a), which provides a summary of four PPD derivatives. It has been augmented with more information on PPD (Stahl et al. 1990), a PPD derivative (Prosser et al. 2017a), and other authoritative reviews of toxicity (OECD 2004; ECHA 2023b). The references are notes as footnotes to the table. The most conservative toxicity values are shown, as is the entity that conducted the referenced test. The cells are color-coded based on GHS criteria (U.S. EPA 2011). Blank cells represent data gaps. Toxicity values from dossiers were accepted as reliable information pursuant to section 69501.1(a)(57)(A)(3).

PPD Derivative (CASRN)	Acute Fish Toxicity (mg/L) 96 h LC_{50}	Chronic Fish Toxicity (mg/L)	Acute Aquatic Invert. Toxicity (mg/L) 48 h EC_{50} or LC_{50}	Chronic Aquatic Invert. Toxicity (mg/L)	Algal Toxicity (mg/L) 96 h EC_{50} (unless noted)
PPD (106-50-3)	0.06 [a] vH	–	0.28 [a] vH	–	0.28 [a] vH
IPPD (101-72-4)	0.41 [b] vH Monsanto 1979	–	0.69*[b] vH Currenta 2010	0.028*[b] 21d NOEC vH Currenta 2010	2.6*[b] 72 h ErC_{50} H Currenta 2010
6PPD (793-24-8)	0.028 [c] vH MITI 1999	0.0037 [c] 30d NOEC vH MITI 2002	0.23 [c] vH MITI 1999	0.013 [d] 28d LC_{50} vH	0.6 [e] vH Monsanto 1978
7PPD (3081-01-4)	0.3 [c] vH Monsanto 1983	–	0.2 [c] vH Monsanto 1983	–	–
44PD (101-96-2)	0.24 [c] vH Monsanto 1981	–	0.54 [c] vH MITI 2010	–	0.939 [c] vH MITI 2010
77PD (3081-14-9)	0.06 [c] vH Monsanto 1981	–	0.37 [c] vH Monsanto 1979	–	–
Key	Low (L)	Moderate (M)	High (H)	Very High (vH)	

EC_{50} = effect concentration in 50% of test animals. LC_{50} = lethal concentration in 50% of test animals.

ErC_{50} = the effect concentration that results in a 50% reduction in growth rate of algae.

NOEC = no observed effect concentration

*IPPD's major hydrolysis product, 4-hydroxydiphenylamine, was used in the assays indicated because the half-life of IPPD is 3.9 hrs.

[a] = Stahl et al. 1990. [b] = ECHA 2023b. [c] = ECHA 2020a. [d] = Prosser et al. 2017a. [e] = OECD 2004.

Model results

U.S. EPA's HCD *Hazard* module incorporates the TEST modeling software to predict the acute aquatic toxicity of chemicals for which there is no hazard information from either authoritative sources or screening sources. TEST calculates multiple QSAR predictions based on five methods – Hierarchical Clustering, Single Model, Group Contribution, Nearest Neighbor, and Consensus (Martin 2017). The HCD *Hazard* module reports the TEST prediction based on the Consensus method (an average of the predicted toxicities from the other four QSAR methods) (Vegosen and Martin 2020). According to Martin (2020), the Consensus method produces the best prediction accuracy for acute aquatic toxicity. TEST predictions for acute aquatic toxicity are based on median 96-hour fathead minnow LC_{50} and 48-hour *Daphnia magna* LC_{50} data from the ECOTOX data set and are ultimately compared to GHS criteria to get a hazard score (Vegosen and Martin 2020). If an LC_{50} cannot be predicted for either fathead minnow or *Daphnia magna*, TEST provides a score of "not available."

91% of PPD's derivatives (1,674 of 1,849) have acute aquatic toxicity hazard scores solely as a result of QSAR predictions using TEST in the HCD (U.S. EPA 2023a). Approximately 30% of these (496 of 1,674) have an HCD acute aquatic hazard score of *high* based on TEST predictions, and 42% (705 of 1,674) have a score of *very high* (Table 2). The HCD reports that 11% of PPD derivatives have a *low* hazard score based on TEST predictions (U.S. EPA 2023a).

Mechanisms

One of the seminal papers in developing models for aquatic toxicity states, "It is well known that reactive chemicals are lethal at lower concentrations than unreactive compounds with equal K_{OW} values" (Hermens 1990). While the exact mechanisms of aquatic toxicity have yet to be elucidated, PPD derivatives, as well as their oxidation products, are known to be reactive (see Evidence for Dermatotoxicity). In making computer models for aquatic toxicity, U.S. EPA considers both anilines and amines as having "excess toxicity" compared to what would be predicted based on their absorption and a narcosis mode of action. These chemical classes contain reactive functional groups, indicating that they have a more specific mode of action (Mayo-Bean et al. 2017).

Based on work identifying the oxidation products of PPD (Aeby et al. 2009; Lewis et al. 2013; Meyer and Fischer 2015) and 6PPD (Tian et al. 2021; Seiwert et al. 2022), some of the intermediates are likely to be reactive and, in some cases, act as electrophiles. Electrophiles generally attack nucleophilic centers on proteins and nucleic acids, forming what are often referred to as adducts – biological molecules that have an extra chemical bonded to them. Molecules that are adducts may not function properly.

Conclusion

Most of the PPD derivatives with experimental data are categorized as having *very high* acute aquatic toxicity across all trophic levels. By definition, PPD derivatives are structurally similar; therefore,

pursuant to 69502.2(b)(1)(D), SCP can use reliable information to extrapolate hazard traits to data-poor chemicals. U.S. EPA's TEST tool further substantiates the concern for acute aquatic toxicity across the class because the majority of chemicals are classified as having *high* or *very high* acute aquatic toxicity. Because acute aquatic toxicity has the potential to impair wildlife survival, these chemicals meet the criteria in CCR, Title 22, section 69404.9 for inclusion on DTSC's Candidate Chemicals List.

3.2. Cumulative Effects

Reference: California Code of Regulations, Title 22, section 69502.2(b)(1)(A)(3)

Cumulative effects occur from exposures to chemicals with the same or similar hazard traits or environmental or toxicological endpoints.

Other toxicants may exacerbate the hazard traits of PPD derivatives. The information presented below suggests that some cumulative impacts may occur, which supports our rationale for adding PPD derivatives to the Candidate Chemicals List.

Dermatotoxicity

Allergic sensitization does not lend itself to the traditional understanding of cumulative health impacts, which ordinarily pertains to something like multiple liver toxicants accelerating the development of liver disease. For allergic responses, the concern is cross-sensitization, where an individual develops allergic responses to related chemicals and the products that contain them. Some PPD derivatives induce cross-reactivity in sensitized individuals (Bacharewicz-Szczerbicka et al. 2019). The FDA recognizes that people who have been sensitized to PPD may have allergic responses to similar chemicals in rubber and latex; local anesthetics like benzocaine and procaine; sulfonamide, sulfone, and sulfa-based antibiotics; and *para*-aminobenzoic acid, an ingredient in some sunscreens (U.S. FDA 2022c). Herve-Bazin et al. (1977) studied cross-reactivity among PPD derivatives, testing eight individuals who had become sensitized to IPPD at work. All eight had cross-reactivity to CPPD (Herve-Bazin et al. 1977). In a separate experiment, they challenged 15 IPPD-sensitized subjects with 6PPD, and all 15 had an allergic response (Herve-Bazin et al. 1977). Similarly, IPPD-sensitized subjects also cross-reacted with PPD, although at a lower frequency and reduced response compared to IPPD (Herve-Bazin et al. 1977). Thus, a rubber industry worker exposed to 6PPD might experience allergic contact dermatitis through an inductive exposure to PPD through hair dye, for example. Sensitizing exposures to PPD derivatives – at work or through product use – may increase the chance of allergic reactions to other PPD derivatives in, or released from, products, due to the potential of cross-sensitization.

Acute Aquatic Toxicity

Wildlife survival impairment is a broad hazard trait. Many aquatic toxicants other than PPD derivatives may have cumulative impacts that further reduce the viability of wild populations. For example, urban stormwater is a complicated mix of contaminants that can impact surface water quality (Young et al. 2018; Peter et al. 2020; Saifur and Gardner 2021; Johannessen et al. 2021b) and has the potential to harm aquatic organisms. The toxicants carried by stormwater may exacerbate the aquatic toxicity of PPD derivatives to exposed biota (de Zwart et al. 2018). Adverse impacts caused by cumulative exposures would be important to explore in a more focused regulatory context, such as listing a Priority Product, but they do not form the primary basis for adding PPD derivatives to the Candidate Chemicals List.

3.3. Physicochemical Properties

Reference: California Code of Regulations, Title 22, section 69502.2(b)(1)(A)(4)

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.

While the primary rationale for adding PPD derivatives to the Candidate Chemicals List is based on toxicity, physiochemical properties can also play an important role in potential adverse impacts. They are embedded within TEST's algorithms and are used to help predict toxicity. For example, a chemical's octanol-water partition coefficient (K_{OW}) and water solubility influence its aquatic toxicity hazard score (U.S. EPA 2012; U.S. EPA 2015b; Martin 2020; Vegosen and Martin 2020). Furthermore, we rely on physicochemical properties to help predict how chemicals will behave in the environment, as discussed in the following section. However, in this section we will not elaborate on all the physicochemical properties specified in CCR, Title 22, section 69407.2.

3.4. Environmental Fate

Reference: California Code of Regulations, Title 22, section 69502.2(b)(1)(A)(5)

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.

CCR, Title 22, Chapter 54 takes environmental fate parameters into account when considering exposure potential hazard traits. While environmental fate is not a part of the primary basis for adding PPD derivatives to the Candidate Chemicals List, there is troubling data regarding their potential for bioaccumulation and persistence in their dominant environmental compartment (soil).

Experimental data for the 1,849 identified PPD derivatives is scarce. To fill data gaps, we used U.S. EPA's TEST and OPERA QSAR modeling tools to estimate relevant physicochemical properties to better understand the environmental fate of PPD derivatives. OPERA, a collaboration between the National Toxicology Program (NTP) and U.S. EPA, is designed to predict physicochemical properties and environmental fate parameters (NTP 2023). More information about QSAR can be found in the [Reliable Information Regarding Hazard Traits and Toxicological Endpoints](#) section. In addition, this section includes environmental fate information from ToxServices' GreenScreen® Assessments, commissioned by Washington State's Department of Ecology, for five PPD derivatives (CPPD, IPPD, 6PPD, 7PPD, and 77PD). The GreenScreen® Assessments used U.S. EPA's Estimation Program Interface Suite (EPI Suite) software to predict behavior in different environmental compartments and potential to bioaccumulate or persist in the environment (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d; ToxServices, LLC 2021e).

Media Partitioning

Media partitioning helps to predict where a chemical will go when it is released into the environment. Chemicals generally have differential affinities for water or hydrophobic compartments, like biological tissue or sediment. K_{OW} (octanol-water partition coefficient; also known as P) and K_{OC} (soil adsorption coefficient) are metrics that drive these predictions (U.S. EPA 2012). Based on the models of these parameters, the class of PPD derivatives has some affinity for water but greater affinity for tissues, soils, and sediments.

K_{OW}

Experimental and modeled data of log K_{OW} suggest that PPD derivatives have a greater affinity for hydrocarbons and fats compared to water. Chemicals with a log K_{OW} between 2 and 4 tend to be absorbed through biological membranes, and OPERA predicts a median log K_{OW} of 3.0 for this class (U.S. EPA 2012; U.S. EPA 2023d).

Water Solubility

PPD derivatives are generally expected to be slightly soluble in water (U.S. EPA 2012; U.S. EPA 2023d). Of the few experimental water solubilities we located for PPD derivatives, one is very soluble in water (> 10,000 ppm) and the other is negligibly soluble in water (< 0.1 ppm) (U.S. EPA 2012; U.S. EPA 2023d). Of the 1,849 chemicals that fit the proposed definition, TEST and OPERA were able to predict water solubilities for 1,560 and 1,806 PPD derivatives within their domains of applicability, respectively (Table 5). The water solubility results for TEST and OPERA generally agree and predict that the majority of modeled PPD derivatives will be slightly soluble in water (U.S. EPA 2012; U.S. EPA 2023d). Results reported for five PPD derivatives in GreenScreen® assessments completed using EPI Suite largely agreed with those from TEST and OPERA (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d; ToxServices, LLC 2021e).

Table 5: Water solubilities for PPD derivatives predicted by TEST and OPERA (U.S. EPA 2012; U.S. EPA 2023d).

Water Solubility	Range	Number (%) of PPD Derivatives scored in TEST	Number (%) of PPD Derivatives scored in OPERA
Negligibly soluble	< 0.1 ppm	126 (8.1%)	73 (4.0%)
Slightly soluble	0.1 – 100 ppm*	943 (60.4%)	1,071 (59.3%)
Moderately soluble	100 – 1,000 ppm	306 (19.6%)	345 (19.1%)
Soluble	1,000 – 10,000 ppm	177 (11.3%)	220 (12.2%)
Very soluble	> 10,000 ppm	8 (0.5%)	97 (5.4%)
	Total	1,560 (100%)	1,806 (100%)

*median of 17.9 ppm for TEST and 24.7 ppm for OPERA

Affinity to Soil, Sediment, and Sludge

PPD derivatives are predicted to have moderate affinity to soil, sediment, and sludge compared to water because of their estimated soil adsorption coefficients (K_{OC}) (Table 6). Of the 1,849 known chemicals that fit the proposed definition, OPERA was able to predict log K_{OC} values for 1,806 PPD derivatives within its domain of applicability. OPERA predicts a median log K_{OC} of 3.1 where nearly half (47.8%) have log K_{OC} values between 2.45 and 3.45, suggesting a greater affinity for soil, sediment, and sludge than for water (U.S. EPA 2012; U.S. EPA 2023d). On the extremes of this data spread, 16.1% of PPD derivatives are predicted to have very strong adsorption to soil, sediment, and sludge, while only 0.2% have negligible adsorption (U.S. EPA 2012; U.S. EPA 2023d).

Table 6: Soil Affinity (log K_{OC}) values for PPD derivatives predicted by OPERA. Log K_{OC} ranges are based on U.S. EPA's EPI Suite guidance (U.S. EPA 2012; U.S. EPA 2023d).

Soil / Sediment / Sludge Adsorption	Migration to Ground Water	Log K_{OC} Range	Number (%) of PPD Derivatives scored in OPERA
Negligible	Rapid	< 1.5	4 (0.2%)
Low	Moderate	1.5 – 2.45	431 (23.9%)
Moderate	Slow	2.45 – 3.45*	863 (47.8%)
Strong	Negligible to slow	3.45 – 4.4	218 (12.1%)
Very strong	Negligible	> 4.4	290 (16.1%)
		Total	1,806 (100%)

*median = 3.1

Fugacity Modeling

Fugacity is the tendency for a substance to transport between environmental compartments (e.g., air, water, sediment, and soil) (U.S. EPA 2015c). GreenScreen® assessments used Level III Fugacity Models (MCI Method) embedded within U.S. EPA's EPI Suite software to predict the ultimate partitioning of five PPD derivatives (Table 7). Results suggest that when these derivatives are released into the environment, they will primarily partition to soil with proportions between 65% and 85.1% (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d;

ToxServices, LLC 2021e). They are also predicted to partition to water with proportions between 9.58% and 15.1%. Water is a relevant compartment because of aquatic toxicity and the wildlife survival impairment hazard trait (see [Evidence for Wildlife Survival Impairment](#)). Finally, the five modeled PPD derivatives are predicted to partition to sediment with proportions between 0.8% and 22.9%, where they may adversely affect species like *Hyalella Azteca*, *T. tubifex* (sludge worms) and mussels. Some pollutants are known to sequester in sediments that act as chemical reservoirs, reintroducing them into ecosystems at a later time (U.S. EPA 2014).

Table 7: Fugacity model results for five PPD derivatives using U.S. EPA's EPI Suite software (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d; ToxServices, LLC 2021e).

PPD Derivative (CASRN)	Partition to Air (%)	Partition to Water (%)	Partition to Sediment (%)	Partition to Soil (%)
CPPD (101-87-1)	0.0410	15.1	0.815	84.1
IPPD (101-72-4)	0.0086	12.0	2.980	85.1
6PPD (793-24-8)	0.0449	13.3	17.60	69.1
7PPD (3081-01-4)	0.0157	9.58	22.40	68.0
77PD (3081-14-9)	0.0625	12.0	22.90	65.0

Bioaccumulation

Modeled data suggest that some PPD derivatives may bioaccumulate, which could increase the duration and likelihood of exposure to aquatic organisms. OPERA predicts that 491 (27.2%) of the 1,849 identified PPD derivatives have log K_{OW} values greater than or equal to 4 (log $K_{OW} \geq 4$), the threshold for bioaccumulation set forth in CCR section 69405.2. Bioconcentration factor (BCF) is another indicator used to predict whether a chemical will accumulate in biological tissue. Predicted BCF values suggest that only a small fraction of PPD derivatives will bioaccumulate. TEST and OPERA predicted BCFs for 1,373 and 1,806 PPD derivatives within their domains of applicability, respectively. Of these, 4 (0.3%) from TEST and 35 (1.9%) from OPERA are predicted to have BCFs greater than 1,000, the threshold for bioaccumulation set forth in CCR, Title 22, section 69405.2 (U.S. EPA 2023d). While experimental data would be ideal to resolve these discrepancies between predictions for bioaccumulation, BCFs are considered more realistic measurements of bioaccumulation compared to K_{OW} (Decision et al. 2014).

GreenScreen Assessments for five more-studied PPD derivatives score their bioaccumulation potential between *very low* and *high*. A measured log K_{OW} of 2.77 justified IPPD's *very low* bioaccumulation score

(ToxServices, LLC 2021a), while a measured BCF of 1,500 – 1,700 for N-(1-methylheptyl)-N'-phenylbenzene-1,4-diamine (CASRN 15233-47-3), which is a PPD derivative surrogate, provided the rationale for 6PPD's *high* bioaccumulation score (ToxServices, LLC 2021d). Modeled information provides the rationale for CPPD's and 77PD's bioaccumulation scores of *high* and *medium*, respectively (ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021e). Due to the variability of these results, bioaccumulation is not one of the hazard traits supporting the addition of PPD derivatives to the Candidate Chemicals List.

Environmental Persistence

Modeled data suggest that some PPD derivatives may be environmentally persistent, which could increase the duration and likelihood of exposure to organisms in the environment. The GreenScreen® Assessments commissioned by Washington State's Department of Ecology scored five PPD derivatives *high* for environmental persistence because modeling predicted 75-day half-lives in soil, their predicted dominant compartment (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d; ToxServices, LLC 2021e). Importantly, these chemicals are also predicted to persist in sediment, with half-lives of 337 days (Table 8). SCP's regulatory threshold for persistence in soil and sediment is two months (Table 8) (22 CCR 69405.3). Sediment is a relevant medium for chemicals associated with tires and tire wear particles because sensitive benthic species, including mussels, live in this compartment (Rypel 2022). In addition, the BIOWIN modeling Ready Biodegradable Predictor embedded within U.S. EPA's EPI Suite software predicted that these PPD derivatives would not be readily biodegradable (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d; ToxServices, LLC 2021e). However, the half-lives predicted by OPERA through the CompTox Chemicals Dashboard indicate that PPD derivatives will not generally be persistent, although the medium is not specified. Therefore, persistence is not part of the basis for adding PPD derivatives to the Candidate Chemicals List.

Table 8: Predicted half-lives for five PPD derivatives (CPPD, IPPD, 6PPD, 7PPD, and 77PD) in air, water, sediment, and soil. Results completed by GreenScreen® Profilers using Level III Fugacity Model (MCI Method) embedded within U.S. EPA's EPI Suite software (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d; ToxServices, LLC 2021e). Regulatory threshold for environmental persistence is defined in CCR, Title 22, section 69405.3.

Environmental Medium	Half-Life	Regulatory Threshold for Environmental Persistence	Prediction
Air	1.13 to 2.04 hrs.	> 2 days	Not persistent in air
Water	37.5 days	40 – 60 days	Not persistent in water
Sediment	337.5 days	2 months	Persistent in sediment
Soil	75 days	2 months	Persistent in soil

3.5. Populations That May Be Adversely Impacted

Reference: California Code of Regulations, Title 22, section 69502.2(b)(1)(A)(6) and 69502.2(b)(1)(B)

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

Aquatic organisms at all trophic levels have the potential to be impacted by the release of PPD derivatives into their habitats because of the high acute aquatic toxicity and possible chronic aquatic toxicity. The toxicity of PPD derivatives to fish is best represented in the literature, but toxicity to aquatic invertebrates such as freshwater mussels, daphnia, and amphipods has also been documented (see Evidence for Wildlife Survival Impairment). Sensitive subpopulations include *endangered* and *threatened* aquatic species that may be exposed to this class of chemicals and their transformation products. The transformation product of most concern is 6PPD-quinone because of its toxicity to some members of the salmonid family, which includes salmon, trout, and char. 6PPD-quinone's toxicity to salmonids ranks in descending order of sensitivity: coho salmon (Tian et al. 2022); brook trout (Brinkmann et al. 2022); rainbow trout/steelhead (Brinkmann et al. 2022); and Chinook salmon, which are marginally sensitive (French et al. 2022; Greer et al. 2023). Other than brook trout, these species are native to California, and some of their populations are potentially at risk (Table 9). The trout species whose ranges are shown in Figure 2 are endemic to California and have yet to be tested for sensitivity to PPD derivatives (see Figure 6 in DTSC 2022). These populations may be at risk because they are small and geographically isolated. Intriguingly, some salmonids (chum, sockeye, Dolly Varden, cherry salmon, and Arctic-char) are unaffected by 6PPD-quinone (Scholz et al. 2011; Brinkmann et al. 2022; French et al. 2022; Hiki and Yamamoto 2022; Greer et al. 2023; Greer et al. 2023).

Thus far, few North American fish species outside of the salmonid family have been tested for toxicity. Other endangered fish may be sensitive to the PPD derivatives, their transformation products, and 6PPD-quinone specifically. However, since the effects of 6PPD-quinone on other species is unknown, we focus on the salmonids. Table 9 lists salmonid populations that are listed as threatened or endangered by the California Department of Fish and Wildlife, the U.S. Department of Fish and Wildlife, or the National Oceanographic and Atmospheric Administration (California Natural Diversity Database 2023).

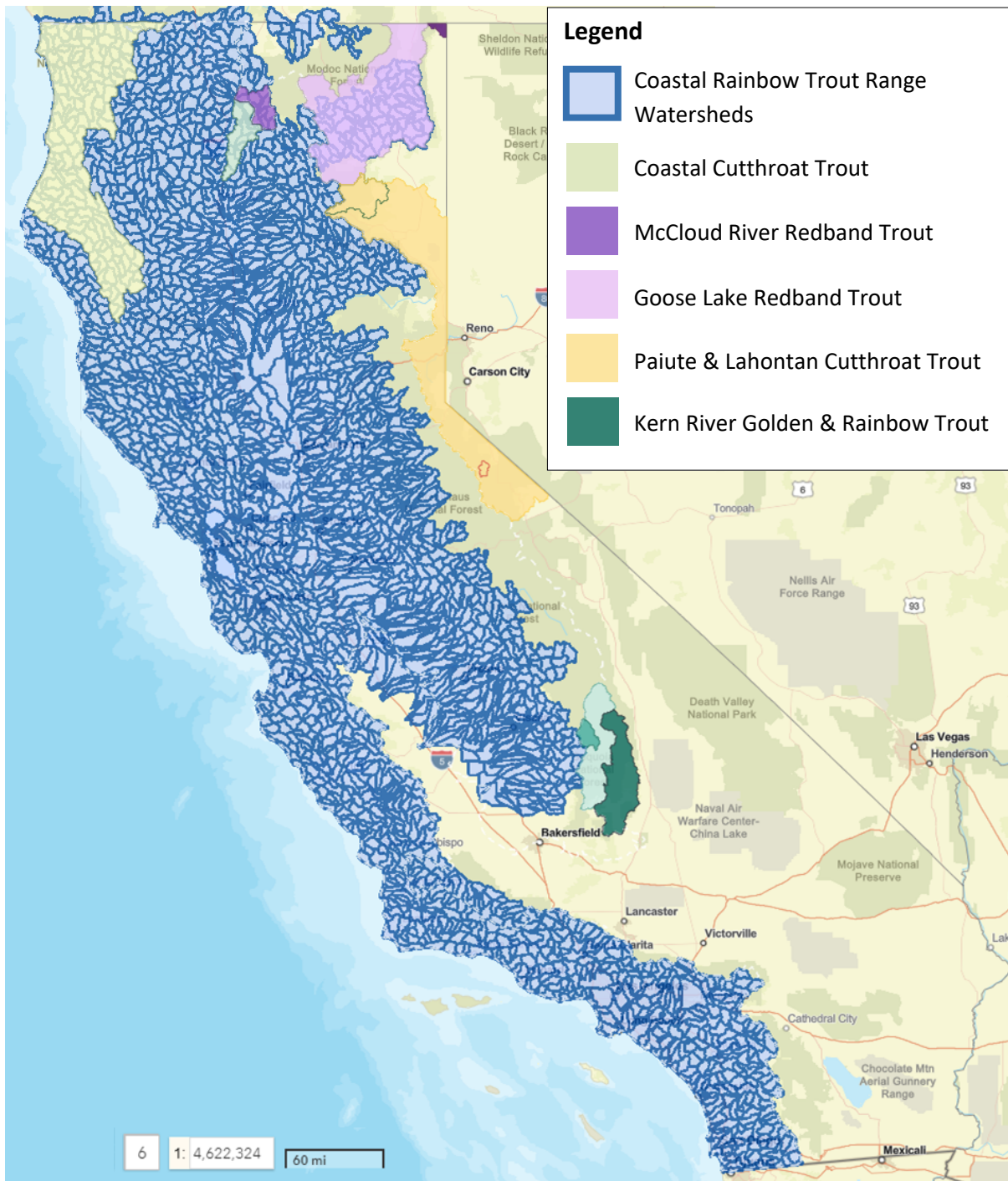*Figure 2. Range of salmonids in California as generated by BIOS (CDFW 2023). The coastal rainbow trout range [ds1282] (Santos 2014) delineates watersheds within the rainbow trout range. Coho and Chinook salmon ranges fall within the same area and are not mapped separately. The colored areas represent the historic ranges of endemic trout species [ds440] (CDFW 2017), as indicated by the legend.*

Table 9: Salmonids designated as threatened or endangered in California (California Natural Diversity Database 2023).

Species	Evolutionarily significant unit (ESU)	Status
Bull trout (*Salvelinus confluentus*)	Considered extirpated (i.e., extinct)	State Endangered
Chinook salmon (*Oncorhynchus tshawytscha*)	Sacramento River winter-run, Central Valley spring-run, Upper Klamath and Trinity Rivers	State listed
Coho salmon (*Oncorhynchus kisutch*)	Southern Oregon/Northern California, Central California coast	State listed
Steelhead (*Oncorhynchus mykiss irideus*)	Northern California DPS summer-run, Other populations are candidates for state listing and federally listed	State Endangered
Paiute cutthroat trout (*Oncorhynchus clarkii seleniris*)	–	Federally Threatened
Lahontan cutthroat trout (*Oncorhynchus clarkii henshawi*)	–	Federally Threatened
Little Kern golden trout (*Oncorhynchus mykiss whitei*)	–	Federally Threatened

State listed indicates that various populations may be listed as threatened or endangered. For the sake of brevity, we are not detailing which populations have which designation.

PPD derivatives have not been extensively tested on invertebrates; however, 6PPD ranked as having both *very high* acute and chronic aquatic toxicity to fatmucket mussels and wavy-ray lampmussels (Prosser et al. 2017b). Freshwater mussels face significant challenges in California and around the world. While none of the three or four species native to California are listed by the state as threatened or endangered, the abundance of mussels in California has declined (Rypel 2022). Researchers identified 116 California sites where mussels were present in the historical record; at the time of the survey, in 2015, mussels were only found at 47% of those sites (Rypel 2022). Mussels have been extirpated from 13 of the 14 streams in southern California (Rypel 2022). Beyond California, freshwater mussels represent the largest group of animals in the U.S. listed as *threatened* or *endangered* under the Endangered Species Act (U.S. FWS 2022). Globally, both the number of mussel species and their abundance have precipitously declined (Aldridge et al. 2023) due to a combination of factors including pollutants, climate change, invasive species, and habitat destruction from dams and channelization of streams (Williams et al. 1993; Aldridge et al. 2023). In 1993, 213 of the 297 native freshwater mussel species in the U.S. and Canada were listed as *endangered*, *threatened*, or of special concern (Williams et al. 1993). This wholesale decline is much more pronounced than those in any terrestrial species (Williams et al. 1993). Mussels are a critical part of the food web, provide important ecosystem services, and are critically important to many Native American Tribal Nations (Williams et al. 1993; Rypel 2022; Aldridge et al. 2023). During specific life stages, mussels are benthic and are likely to have

contact with the sediment where PPD derivatives are likely to partition. Thus, freshwater mussels represent a sensitive subpopulation based on the toxicity of the PPD derivatives.

Workers who manufacture or use PPD derivatives represent another population that may be impacted by the chemicals' toxic health effects. Occupational studies involving hairdressers and barbers have reported PPD skin sensitization rates from 3.7% to 85% in (Cosmetic Ingredient Review 2007). Occupational studies involving hairdressers and barbers have reported PPD skin sensitization rates from 3.7% to 85% in (Cosmetic Ingredient Review 2007). Herve-Bazin et al. (1977) identified 42 cases of occupational IPPD sensitivity among tire manufacturing workers, tire dealers, or in automobile transport and servicing sectors (e.g., drivers and mechanics). Among the IPPD-sensitized workers, the researchers further tested individuals for cross reactivity to other PPDs. Eight out of eight individuals (100%) cross-reacted to CPPD (Herve-Bazin et al. 1977). Forty of the workers were also tested with PPD; 15 individuals (37%) had cross reactivity, although the reactions were generally not as severe (Herve-Bazin et al. 1977). Bacharewicz-Szczerbicka et al. (2019) patch-tested patients with allergic contact dermatitis and identified 128 who were specifically allergic to PPD. 46% of the PPD-sensitized individuals (59 people) had a reliable or probable association of dermatitis based on occupational exposures; these individuals worked as mechanics, hairdressers, farmers, and in jobs involving contact with printing ink. The same study identified 34 patients with occupationally associated allergic responses to IPPD (Bacharewicz-Szczerbicka et al. 2019). The study was broad survey of 4,087 patients with allergic contact dermatitis, those sensitized to PPD or IPPD were a small fraction of the total cohort (Bacharewicz-Szczerbicka et al. 2019).

3.6. Degradation, Reaction, or Metabolic Products of Concern

Reference: California Code of Regulations, Title 22, section 69502.2(b)(1)(A)(7)

A 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 may cause different adverse impacts from those of the parent chemical. In some cases, a 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 chemical's release to the environment.

PPD derivatives are inherently reactive compounds and can be reasonably anticipated to generate transformation products that are released to, or form in, the environment (Klöckner et al. 2021; Seiwert et al. 2022; Hu et al. 2022; Rossomme et al. 2023). For example, when exposed to ambient oxygen (O_2) and ozone (O_3), PPD and 6PPD both form a variety of transformation products, many of which are also reactive and toxic (e.g., 6PPD-quinone) (Lewis et al. 2013; Meyer and Fischer 2015; ECHA 2021; Seiwert et al. 2022). Numerous PPD oxidation products act as reactive haptens and bind to biological molecules. These can be responsible for allergic contact dermatitis (e.g., benzoquinone

diimine, benzoquinone, and Bandrowski's base—see [Evidence for Dermatotoxicity](#)) (Meyer and Fischer 2015).

One 6PPD transformation product, 6PPD-quinone, has an LC_{50} of 41 ng/L in coho salmon hatchlings and is one of the most potent aquatic toxicants recorded (Lo et al. 2023). 6PPD-quinone kills coho within just a few hours of exposure (Scholz et al. 2011; Tian et al. 2021) and has been associated with mass die-offs of the species (Tian et al. 2021; Tian et al. 2022). Research that involved exposing juvenile coho salmon to roadway runoff has implicated blood-brain barrier disruption as the toxic mode of action for 6PPD-quinone (Blair et al. 2021). Another hypothesis is that 6PPD-quinone causes mitochondrial uncoupling (Mahoney et al. 2022), which disrupts the energetics of cells in susceptible fish. Other suspected toxic pathways that have been observed include neurodegeneration and intestinal barrier disruption in *Caenorhabditis elegans* (Hua et al. 2022; Hua et al. 2023) and DNA adduct formation in cultured human cells and capelin fish (Wu et al. 2023).

Research conducted in China has detected some PPD derivatives and their quinone transformation products in environmental media. These studies included 6PPD and 6PPD-quinone but also tested for a broader array of PPD derivatives (see [Environmental Monitoring Data](#)). The hazards associated with these PPD derivative quinones are unknown, but we understand that quinones in general are necessary in some biological systems (e.g., cellular respiration) and could be toxic in others (e.g., benzene metabolism) (Bolton et al. 2000; Turunen et al. 2004; Wang et al. 2015). Broadly speaking, quinones can induce many hazardous effects in exposed tissue (Bolton et al. 2000). For example, quinones can act as Michael acceptors and cause damage to cellular proteins or DNA through electrophilic alkylation. The high reduction oxidation reaction (redox) activity of quinones also allows them to "redox cycle" between semiquinone and hydroquinone, which generates reactive oxygen species (ROS). These ROS (e.g., superoxide and hydrogen peroxide) subsequently cause molecular and cellular damage by oxidizing macromolecules like proteins, nucleotides, and lipids (Bolton et al. 2000).

Our definition of the PPD derivatives class aims to encompass a group of structurally similar molecules that share reactivity (see [Chemical Definition](#)). Toxic transformation products formed from PPD and 6PPD suggest the increased potential for analogous products to form from other PPD derivatives. Although structural features beyond the PPD moiety may prevent quinone formation in other PPD derivatives, the underlying PPD moiety itself is present in each. Therefore, DTSC finds it reasonable and necessary to consider the potential for PPD derivatives to generate other transformation products of concern.

3.7. Reliable Information Regarding Hazard Traits and Toxicological Endpoints

Reference: California Code of Regulations, Title 22, sections 69501.1(a)(57) and 69502.2(b)(3)

The SCP Regulations direct the Department to consider potential adverse impacts based on reliable information.

We have relied on information from governmental agencies such as U.S. EPA and the European Chemicals Agency, as well as information from peer-reviewed studies, to establish the hazard traits of several known PPD derivatives. The highest-quality information has been used whenever available, and we have prioritized authoritative sources over screening data and modeled toxicity data.

Pursuant to CCR, Title 22, section 69502.2(b)(1)(D), we have relied on the hazard traits of chemicals for which there is reliable information and extrapolated it to structurally similar chemicals for which there is insufficient data. We have used U.S. EPA's Hazard Comparison Dashboard (HCD) to approximate the number of chemicals that fit the parameters of the proposed definition and to integrate hazard data from 25 publicly available sources selected by U.S. EPA (Vegosen and Martin 2020). The HCD is a screening tool intended to allow regulators to rapidly compare chemical structures and hazards (Vegosen and Martin 2020). The HCD also integrates U.S. EPA's TEST, which provides state-of-the-science quantitative structure-activity relationship (QSAR) information on chemicals for which there are data gaps (Martin 2020). Similar to the extrapolation described in CCR 69502.2(b)(1)(D), QSARs are mathematical models used to predict measures of toxicity using the physical or structural characteristics of similar chemicals (Martin 2020). Modeled data from QSAR methods are considered "other scientific information" (22 CCR 69501.1(a)(57)) and have been used to fill hazard trait data gaps because many PPD derivatives do not have authoritative or screening data available. The use of "other scientific information" is necessary because there are scientific methods that are not "studies" (such as QSAR) but are important in supporting the identification of Candidate Chemicals (DTSC 2013).

TEST requires that, for a hazard endpoint to be successfully modeled, at least two different QSAR methods must produce a result (Martin 2020). If a chemical's molecular descriptors are outside the domain of applicability for all the models in TEST, a prediction cannot be made and a score of "inconclusive" is provided in the HCD. Thus, the predictive power of the software is improved by only producing results within a threshold of agreement between individual methods. The paucity of information on toxicity drives the need for predictive toxicology methods, such as QSAR (Smith et al. 2020). Of the 1,849 identified chemicals in this class, only 31 had aquatic toxicity hazard scores based on authoritative or screening sources (5 authoritative, 26 screening). The remaining 1,811 chemicals had no data available from the public sources that U.S. EPA mines for information.

There are still significant uncertainties in using available QSAR models to predict hazards, due to varying reliability and application ranges (United Nations 2021). The GHS states that "reliability decreases with increasing complexity of chemical structure, unless a QSAR has been derived for a narrowly defined set of chemicals similar in structure to the candidate substance." Specific to acute aquatic toxicity, predictions may be "in error by several orders of magnitude" and may underestimate toxicity in the case of baseline toxicity if an inappropriate QSAR model is used (United Nations 2021). TEST has undergone statistical, external validation to determine prediction accuracy and coverage (Martin 2017). For both the 96-hour fathead minnow LC_{50} and the 48-hour *Daphnia magna* LC_{50} models within TEST, the external validation results indicate that the predicted results should be used with caution since the prediction statistics did not satisfy all conditions for acceptable predictive power (Martin 2017). Nevertheless, more than 80% of our proposed PPD derivatives have acute aquatic hazard scores of *medium*, *high*, or *very high* based on TEST predictions performed in the HCD, indicating there are concerns for this class, despite uncertainties.

We have used the HCD as intended and pursuant to CCR 69501.1(a)(57)(B). As described by Vegosen and Martin (2020), prioritization of chemicals for further assessment is an explicitly stated purpose for the HCD. Such is also the goal of adding chemicals to the Candidate Chemicals List. Using the HCD to identify chemicals that warrant designation as Candidate Chemicals aligns with this stated purpose for the HCD because the Candidate Chemicals List imposes no regulatory requirements.

OPERA is another QSAR model that has been used to predict the environmental fate of PPD derivatives. OPERA is the product of a collaboration between the National Toxicology Program and U.S. EPA and is designed to predict physicochemical properties and environmental fate parameters (NTP 2023). We accessed OPERA through U.S. EPA's CompTox Chemicals Dashboard and used it as intended and pursuant to CCR 69501.1(a)(57)(B). The OPERA modeling procedure was developed with the OECD's five principles for QSAR models in mind, which include defined endpoints; unambiguous algorithms; defined applicability domains; appropriate measures for goodness-of-fit, robustness, and predictability; and a mechanistic interpretation, when possible (Mansouri et al. 2018).

DTSC has therefore determined that the data supporting the potential for PPD derivatives to contribute to or cause adverse impacts qualifies as reliable information and meets the standard set forth in the SCP Regulations.

4.   EXPOSURE INFORMATION THAT IS THE BASIS FOR THIS LISTING

Reference: California Code of Regulations, Title 22, sections 69502.2(b)(2)

The SCP Regulations direct the Department to evaluate reliable information demonstrating the occurrence, or potential occurrence, of exposures to the chemical.

4.1. Indicators of Potential Exposure

Identifying a toxic agent's exposure pathways is a crucial step in illuminating its potential to produce adverse effects in a receptor population. The elements of a complete exposure pathway for a toxic agent include an emission source, the media in which it moves, the location of exposure, an exposure route, and a receptor species (U.S. EPA 2016). Available data for commonly used PPD derivatives suggest that less-studied members of this proposed class – despite the expected reactivity of the PPD moiety – are persistent enough to become ubiquitous in the environment or are produced in sufficient quantities to disperse in the environment and result in detections in runoff, river water, wastewater influent and effluent, particulate matter, dust, sediment, and soil (see Environmental Monitoring Data). The following sections outline the indicators of potential exposure that have been identified for PPD derivatives.

Manufacturing

Eight members of the proposed PPD derivatives class are present on U.S. EPA's High Production Volume (HPV) List (Table 10), an indicator of widespread use. Chemicals on the HPV List are produced in or imported into the United States at quantities of one million pounds per year or greater (U.S. EPA 2023e). High production volume indicates a greater potential for environmental release even if the number of industries or manufacturers using HPV PPD derivatives is unclear.

Table 10: PPD derivatives listed as High Production Volume chemicals by U.S. EPA (U.S. EPA 2023e) and known uses (PubChem 2023).

PPD Derivative (CASRN)	Known Uses
PPD (106-50-3)	Hair dye, photographic developing agent, chemical intermediate, vulcanization accelerator, rubber antioxidant
DPPD (74-31-7)	Antioxidant, polymerization inhibitor, copper degradation inhibitor, intermediate for dyes, drugs, plastics, and detergents
IPPD (101-72-4)	Antioxidant
PPPD (101-54-2)	Rubber, dyes, pharmaceuticals, photographic color production
44PD (101-96-2)	Used in gasoline as a gum inhibitor, antioxidant, and stabilizer
6PPD (793-24-8)	Antioxidant, antiozonant
7PPD (3081-01-4)	Antioxidant, chemical reaction regulator
77PD (3081-14-9)	Antioxidant

Potential Sources of Exposure

Reference: California Code of Regulations, Title 22, section 69502.2(b)(1)(A)(2)

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

PPD derivatives are present in numerous consumer products, which may result in exposures to people and the environment. They have been used by various industries as antidegradants, antioxidants, antiozonants, hair dyes, photographic processing aids, analytical chemistry reagents, standardized chemical allergens, and gasoline additives (U.S. EPA 2021; PubChem 2023; U.S. EPA 2023f). Since 2012, at least 100 PPD derivatives have been listed in U.S. EPA's Chemical Product Database (CPDat), which maps consumer goods, chemicals they contain, and their usage or function (U.S. EPA 2023f; U.S. EPA 2023d). CPDat provides insight into the PPD derivatives that are more likely to be found in products that could lead to environmental release and exposure, even if their prevalence is unclear. As an example, a multitude of products are derived from recycled tires and are potential sources of environmentally released PPD derivatives. Examples include landscape surfacing, mats, tiles, paths, walkways, roofing, and sports surfaces (CalRecycle 2020).

Biomonitoring Data

At least one PPD derivative, 6PPD, and its transformation product, 6PPD-quinone, have been detected in the urine of children (1 – 13 years old), adults (20 – 54 years old), and pregnant women (20 – 41 years old) in southern China (Du et al. 2022). Detection frequencies in these three populations were 60% – 76% for 6PPD and 90% – 100% for 6PPD-quinone. Overall detections ranged between below method quantitation limit (< MQL) and 2.43 µg/g creatinine for 6PPD and between < MQL and 9.17 µg/g creatinine for 6PPD-quinone. Most notably, concentrations of 6PPD and 6PPD-quinone were statistically higher in pregnant women's urine compared to other adults and children (Du et al. 2022).

Table 11: Creatinine-corrected detections of 6PPD and 6PPD-quinone in human urine samples in southern China (Du et al. 2022).

Analyte (CASRN)	Population	Detection Frequency (%)	Median (µg/g creatinine)	Concentration Range (µg/g creatinine)
6PPD (793-24-8)	Children	60	0.015	< MQL – 0.32
	Adults	68	0.020	< MQL – 0.45
	Pregnant Women	76	0.073	< MQL – 2.43
6PPD-quinone (2754428-18-5)	Children	90	0.093	< MQL – 0.64
	Adults	100	0.51	0.078 – 2.87
	Pregnant Women	100	2.76	0.38 – 9.17

Method quantification limits (MQLs) = 0.012 ng/mL for 6PPD and 0.021 ng/mL for 6PPD-quinone. Sample size = 50 for each subpopulation (adults, children, and pregnant women).

Environmental Monitoring Data

PPD derivatives have been detected in a variety of media, including water, wastewater, particulate matter, dust, sediment, soil, and food (Table 12 through Table 18). The detection of more-studied PPD derivatives in multiple media indicate the potential for environmental exposure through all exposure routes that are discussed in the Potential for Adverse Impacts section.

Environmental monitoring, primarily in China, has also detected 6PPD-quinone in fine particulate matter (i.e., $PM_{2.5}$) (Wang et al. 2022), indoor and outdoor dust (Huang et al. 2021; Liang et al. 2022; Deng et al. 2022), river water (Johannessen et al. 2021a; Rauert et al. 2022; Zhang et al. 2023a), sediment (Zeng et al. 2023), and even human urine (Du et al. 2022). Other PPD derivative transformation products have been detected in many of the same environmental media (Liang et al. 2022; Wang et al. 2022; Zeng et al. 2023; Cao 2023).

Runoff

At least five PPD derivatives have been detected in runoff (Cao et al. 2022). Cao et al. (2022) collected samples of runoff 45 or 60 minutes after rain events from a small canal that drains a dense traffic roadway near Hong Kong Baptist University in Hong Kong, China. Detection frequencies for individual PPD derivative samples ranged between 56% and 100%. One PPD derivative, 6PPD, was detected above the instrument detection limit (IDL) in 100% of samples (Cao et al. 2022).

Table 12: PPD derivative results in runoff water samples collected in a dense traffic urban area of Hong Kong, China. Samples collected five days apart from nine locations (Cao et al. 2022).

PPD derivative (CASRN)	Detection Frequency (%)	Median (µg/L)	Concentration Range (µg/L)	IDL (µg/L)
CPPD (101-87-1)	100*	0.01	< IDL – 0.05	Approx. 0.013
DPPD (74-31-7)	56	0.01	0.01 – 0.02	–
DTPD (27417-40-9)	56	0.01	< IDL – 0.01	Approx. 0.089
IPPD (101-72-4)	94	0.01	< IDL – 0.21	Approx. 0.0093
6PPD (793-24-8)	100	0.32	0.21 – 2.71	–

Approximate instrument detection limits (IDLs) provided when applicable to detection results and are calculated as 30% of the reported instrument quantification limit (IQL) from the study.

*One sample analyzed for CPPD was still considered a detection even though its LC-MS peak intensity was lower than the IDL (Cao 2023).

River Water

At least four PPD derivatives have been detected in river waters (Table 13). Zhang et al. (2023) tested surface water from the Zhujiang and Dongjiang Rivers in areas that received urban runoff near Guangzhou, China. They tested for six PPD derivatives, three of which were detected at nanogram per liter concentrations in both rivers (DPPD, DNPD, and 6PPD). DTPD was only detected in one river, and CPPD and IPPD were not detected in either. The authors suspect that the low (ng/L) concentrations of these six substances are an indication of their instability in water and their ease of transformation, as evidenced by the presence of the 6PPD transformation product 6PPD-quinone. 6PPD-quinone's median concentrations in the Zhujiang and Dongjiang Rivers were approximately three times that of 6PPD, with 100% detection frequencies (Zhang et al. 2023a).

Table 13: PPD derivative results in river water samples collected from the Zhujiang and Dongjiang Rivers in Guangzhou, China (Zhang et al. 2023a).

PPD Derivative (CASRN)	River	Detection Frequency (%)	Median (ng/L)	Concentration Range (ng/L)
DPPD (74-31-7)	Zhujiang Dongjiang	26.9 20.0	0.07 0.04	0.05 – 0.07 0.03 – 0.04
DTPD (27417-40-9)	Zhujiang Dongjiang	0 8.00	ND 1.45	ND 1.45 – 1.46
DNPD (93-46-9)	Zhujiang Dongjiang	38.5 40.0	1.41 5.13	< 0.65 – 8.25 0.58 – 19.0
6PPD (793-24-8)	Zhujiang Dongjiang	30.8 48.0	0.48 0.36	0.31 – 1.07 0.27 – 1.29
6PPD-quinone (2754428-18-5)	Zhujiang Dongjiang	100 100	1.51 0.91	0.26 – 11.3 0.29 – 8.12

Limit of detection (LOD) for DTPD = 0.01 ng/L. ND = not detected.

Wastewater

Wastewater Treatment Plants (WWTPs) that fail to completely remove PPD derivatives are sources of their release to aquatic environments (Zhang et al. 2023b). Table 14 displays the study results of eight PPD derivatives sampled in the influent and effluent wastewaters of WWTPs in Canada, Malaysia, and Sri Lanka. In Malaysia and Sri Lanka, IPPD was the only PPD derivative detected in both influent and effluent wastewater while CPPD, DNPD, DPPD, 6PPD and 7PPD were not detected at all (Zhang et al. 2023b). DPPD, DTPD, and PTPD were detected in both influent and effluent waters of Canadian WWTPs under dry-weather conditions. Location-specific detection frequencies for DPPD, DTPD, and PTPD were between 86% and 93% for influent wastewater and between 28% and 55% for effluent wastewaters (Zhang et al. 2021b).

6PPD has also been detected in influent wastewater in Leipzig, Germany (Seiwert et al. 2022). The authors note that, of the combined estimated concentrations for 6PPD and 13 of its transformation products, 6PPD itself accounted for less than 1% of the load (Seiwert et al. 2022).

Table 14: PPD derivative results for WWTP influent and effluent in Malaysia and Sri Lanka (Zhang et al. 2023b), and Canada (Zhang et al. 2021b).

PPD Derivative (CASRN)	# of Sampling Location(s)	Influent DF Range (%)	Influent Range (Median) (ng/L)	Effluent DF Range (%)	Effluent Range (Median) (ng/L)	LOQ (ng/L)
DPPD (74-31-7)	10[a]	88	< 1.0 – 8.8 (0.83)	28	< 0.3 – 1.1 (NA)	–
DTPD (27417-40-9)	10[a]	86	< 1.0 – 12 (0.79)	50	< 0.3 – 3.3 (0.15)	–
IPPD (101-72-4)	3[b]	17 – 43	ND – 60 (ND – 4.2)	42 – 71	42 – 71 (ND – 3.2)	0.022
	2[c]	100	0.63 – 2.4 (1.5 – 2.2)	57 – 100	1.2 – 3.6 (1.9 – 2.4)	–
PTPD (27173-16-6)	10[a]	93	< 0.9 – 13 (1.6)	55	< 0.27 – 3.0 (0.14)	–

DF = detection frequency. Limit of quantification (LOQ) value provided when applicable to detection results. NA = not available. ND = not detected.
[a] = WWTPs in Canada. DF calculated for whole dataset. LOQ range between 0.2 – 1.0 ng/L for influent and 0.06 – 0.3 ng/L for effluent (Zhang et al. 2021b).
[b] = municipal, hospital, and industrial WWTPs in Malaysia. DF calculated by location (Zhang et al. 2023b)
[c] = WWTPs in Colombo and Hikkaduwa, Sri Lanka (Zhang et al. 2023b)

Particulate Matter

At least eight PPD derivatives have been detected in fine particulate matter ($PM_{2.5}$) air samples collected in China (Table 15), with location-specific detection frequencies between 33% and 100%. Within this range, DNPD had the lowest detection frequency (33%), while CPPD, DPPD, DTPD, IPPD, and 6PPD all had at least one sampling location with a detection frequency of 100% (i.e., detected in every sample) (Zhang et al. 2021a; Cao et al. 2022; Wang et al. 2022).

PPD derivative concentrations in $PM_{2.5}$ may correlate with proximity to roads. Wang et al. (2022) collected air samples from one roadside site and two non-roadside sites to assess the potential contribution of vehicle emissions to $PM_{2.5}$ PPD derivative pollution. Statistical analysis determined that the net PPD derivative concentration at the roadside site was significantly higher ($p < 0.001$) than that of a campus building site in the same city (Guangzhou, China). In addition, the highest median of the three locations occurred at the roadside site for seven of the eight PPD derivatives. Even further, six of

the eight highest medians shown in Table 15 are results from the Guangzhou roadside site. While atmospheric samples from Cao et al. (2022) were collected from a tower 40 meters above the ground (Cao et al. 2022), Zhang et al. (2021) did not provide enough information to ascertain sampling distance from roads; they listed locations as universities and government buildings (Zhang et al. 2021a).

Table 15: PPD derivative results for particulate matter (PM$_{2.5}$) (Zhang et al. 2021a; Cao et al. 2022; Wang et al. 2022).

PPD Derivative (CASRN)	# of Sampling Location(s)	Detection Frequency Range (%)	Median Range (pg/m^3)	Concentration Range (pg/m^3)	MDL (pg/m^3)
CPPD (101-87-1)	3[a]	88 – 100	5.70 – 159	< MDL – 672	0.05
	1[b]	75	0.38	< IDL – 0.74	–
	6[c]	83 – 100	0.8 – 2.3	0.1 – 21	–
DNPD (93-46-9)	3[a]	50 – 67	5.22 – 22.5	< MDL – 61.3	0.06
	6[c]	33 – 86	1.1 – 3.7	0.3 – 108	–
DPPD (74-31-7)	3[a]	100	374 – 1250	0.69 – 2,590	–
	1[b]	81	0.5	< IDL – 0.70	–
	6[c]	83 – 100	0.3 – 1	0.1 – 13	–
DTPD (27417-40-9)	3[a]	83 – 100	3.12 – 22.4	< MDL – 27.1	0.50
	1[b]	56	2.86	< IDL – 2.88	–
IPPD (101-72-4)	3[a]	100	125 – 661	0.49 – 3,690	–
	1[b]	100	0.91	0.44 – 2.73	–
	6[c]	71 – 100	0.7 – 1.6	0.2 – 104	–
6PPD (793-24-8)	3[a]	100	81 – 4,040	1.02 – 9,340	–
	1[b]	100	1.78	0.82 – 6.3	–
	6[c]	43 – 100	0.9 – 8.4	0.02 – 487	–
7PPD (3081-01-4)	3[a]	46 – 88	NA – 7.66	< MDL – 75	0.03
77PD (3081-14-9)	3[a]	88 – 96	3.78 – 593	< MDL – 4,150	0.02
	6[c]	42 – 83	19 – 160	0.05 – 7,052	–

Instrument detection limits (IDLs) were not reported by authors. Method detection limit (MDL) provided when applicable to detection results. NA = not available due to detection frequency < 50%.
[a] = Two locations in Guangzhou, China and one in Taiyuan, China in 2017 and 2018 (Wang et al. 2022)
[b] = Hong Kong, China in 2020 and 2021 (Cao et al. 2022)
[c] = Guangzhou, Hangzhou, Nanjing, Shanghai, Taiyuan, and Zhengzhou, China in 2018 and 2019 (Zhang et al. 2021a)

Wang et al. (2022) also detected CPPD-quinone, DPPD-quinone, DTPD-quinone, IPPD-quinone, 6PPD-quinone, and 77PD-quinone in PM$_{2.5}$ from megacities in China. Linear regressions showed significant positive Spearman correlation coefficients (R^2) as high as 0.96 between PPD derivatives and their

associated quinone detections. Codetections of PPD derivatives and their quinones were statistically significant ($p < 0.05$) at all three testing sites for DPPD, IPPD, 6PPD, and 77PD, along with one of three testing sites for CPPD (Wang et al. 2022). Strong codetection correlations can be explained by the formation of quinones from their associated PPD derivatives (Wang et al. 2022).

Dust

At least seven PPD derivatives have been detected in dust samples (Wu et al. 2020; Huang et al. 2021; Deng et al. 2022) (Table 16). The fact that these PPD derivatives have been detected in both indoor and outdoor environments suggest widespread potential for their exposure. While neither DNPD nor DPPD were detected in a Canadian e-waste facility or in North American residential units, both were detected in samples collected from an e-waste recycling workshop in South China (Wu et al. 2020). Liang et al.'s (2022) analysis of antioxidants in e-waste dust, including several PPD derivatives, provides further evidence that PPD derivatives may be used in electronics.

Particle size-dependent PPD derivative distributions suggest an inverse relationship between particulate matter size and PPD derivative concentrations (Deng et al. 2022). For example, dust fractions with diameters under 20 µm contained concentrations of 6PPD, IPPD, and DPPD at levels 9.78, 6.20, and 7.55 times higher, respectively, than did 500 – 1,000 µm dust fractions (Deng et al. 2022).

Table 16: PPD derivative results for dust particles with diameters between 25 and 1000 µm (Wu et al. 2020; Huang et al. 2021; Deng et al. 2022). Samples collected for Liang et al. (2022) were physical dust samples and did not provide particle sizes (Liang et al. 2022).

PPD derivative (CASRN)	# of Sampling Location(s)	Detection Frequency Range (%)	Median Range (ng/g)	Concentration Range (ng/g)	LOQ, MDL, or MQL (ng/g)
CPPD (101-87-1)	1[a]	40	< MQL	< MQL – 19.2	0.58
	4[d]	11.1 – 100	< LOQ – 65	< LOQ – 540	0.17
DNPD (93-46-9)	1[a]	49	< MQL	< MQL – 1,790	11
	3[c]	0	< MDL	< MDL	1.07
	4[d]	83.3 – 100	0.7 – 5.4	< LOQ – 137	0.26
DPPD (74-31-7)	1[a]	53	16	< MQL – 628	3.9
	2[b]	98	17 – 25.2	< LOQ – 697	2.15
	3[c]	0	< MDL	< MDL	0.86
	4[d]	50 – 100	0.2 – 34.9	< LOQ – 217	0.56
IPPD (101-72-4)	1[a]	100	424	18.1 – 6,680	–
	2[b]	89 – 98	28.5 – 34.1	< LOQ – 8,307	2.76
	3[c]	42 – 100	0.11 – 9.93	< MDL – 37.8	0.05
	4[d]	50 – 100	< LOQ – 24.9	< LOQ – 575	2.35
44PD (101-96-2)	1[a]	13	< MQL	< MQL – 12.8	3.2

PPD derivative (CASRN)	# of Sampling Location(s)	Detection Frequency Range (%)	Median Range (ng/g)	Concentration Range (ng/g)	LOQ, MDL, or MQL (ng/g)
6PPD (793-24-8)	1[a]	100	113	13.8 – 1,020	–
	2[b]	100	323 – 356	11.4 – 5,359	–
	3[c]	75 – 100	0.83 – 15.4	< MDL – 37.7	0.06
	4[d]	55.6 – 100	0.3 – 241	< LOQ – 429	0.11
77PD (3081-14-9)	1[a]	36	< MQL	< MQL – 243	1.7
	4[d]	18.2 – 55.6	< LOQ – 2	< LOQ – 77.6	0.30

LOQ = limit of quantification. MDL = method detection limit. MQL = method quantification limit. LOQ, MDL, or MQL reported when applicable to detection results.

[a] *= E-waste recycling workshop in South China (Liang et al. 2022)*

[b] *= Road and parking lot in Guangdong, China (Deng et al. 2022)*

[c] *= E-waste facility in Ontario, Canada, and residential houses in Ontario, Canada and Indiana, USA (Wu et al. 2020)*

[d] *= Road, parking lot, vehicle, and house in Guangzhou, China (Huang et al. 2021)*

Sediment

At least seven PPD derivatives have been detected in sediment (Wu et al. 2020; Zeng et al. 2023). Of the four PPD derivatives analyzed in sediment from the Chicago Sanitary and Ship Canal in Illinois (DNPD, DPPD, IPPD, and 6PPD), only one (6PPD) was detected. 6PPD was detected in 70% of samples, with a detection range from below the method detection limit of 0.06 to 1.93 ng/m^3 and a median of 7.7 ng/m^3 (Wu et al. 2020).

Extensive sediment sampling in China has demonstrated a clear spatial trend, with PPD derivative concentrations decreasing from inland urban rivers of the Pearl River Delta to deep-sea locations of the South China Sea (Table 17) (Zeng et al. 2023). The Pearl River Delta provided ideal conditions to better understand the effects of inland PPD derivative emissions on waterbodies because it is one of the most industrialized urban regions in China, with high traffic volumes, and is, hence, a source of PPD derivatives. Zeng et al. (2023) summed the median concentrations of the seven detected PPD derivatives and demonstrated that the net concentrations significantly decreased with distance from urban rivers (i.e., urban rivers > estuary > coast > deep-sea) (Table 17). Only one PPD derivative (DNPD) was not detected in any deep-sea samples. Authors suggest that PPD derivatives may distribute in the environment like many other organic contaminants, binding to sediment in rivers and preferentially adhering to fine-grained particles like silt and clay to be carried to estuaries, coasts, and ultimately deposited in open ocean sediments (Zeng et al. 2023).

Table 17: PPD derivative results for sediment collected from the Pearl River Delta (PRD), the Pearl River Estuary (PRE), coasts of the South China Sea (SCS), and deep-sea regions of the South China Sea (Zeng et al. 2023).

PPD Derivative (CASRN)	Urban River Median (ng/g, dw)	Estuary Median (ng/g, dw)	Coast Median (ng/g, dw)	Deep-Sea Median (ng/g, dw)	MDL (ng/g, dw)
CPPD (101-87-1)	1.38	0.59	0.79	< MDL	0.19
DNPD (93-46-9)	1.90	< MDL	1.03	< MDL	0.22
DPPD (74-31-7)	2.43	2.39	< MDL	< MDL	0.74
IPPD (101-72-4)	1.61	0.42	0.14	0.26	–
44PD (101-96-2)	3.02	2.27	< MDL	< MDL	0.90
6PPD (793-24-8)	14.4	3.92	1.82	2.66	–
77PD (3081-14-9)	5.58	2.36	1.77	< MDL	0.040
Total*	39.7	14.0	9.47	5.24	–

Method detection limit (MDL) provided when applicable to detection results. dw = dry weight. Number of samples: PRD = 32, PRE = 21, coast = 20, deep-sea = 12.

*Testing location totals calculated as median of per-sample net PPD derivative results, where "< MDL" = 50% of MDL.

Soil

At least five PPD derivatives have been detected in roadside soil (Table 18). Detection frequencies ranged between 72% for DTPD and 100% for DPPD and 6PPD. In addition, the median for 6PPD of 309 ng/g was more than 20 times that of the second highest median of 11.8 ng/g for DPPD (Cao et al. 2022).

Table 18: PPD derivative results in roadside soil in Hong Kong, China. Samples collected 20 days apart from 20 locations on non-rainy days (Cao et al. 2022).

PPD derivative (CASRN)	Detection Frequency (%)	Median (ng/g)	Concentration Range (ng/g)	IDL (ng/g)
CPPD (101-87-1)	92	1.19	0.73 – 15.4	–
DPPD (74-31-7)	100	11.8	3.63 – 84.4	–
DTPD (27417-40-9)	72	4.82	< IDL – 6.78	Approx. 0.089

PPD derivative (CASRN)	Detection Frequency (%)	Median (ng/g)	Concentration Range (ng/g)	IDL (ng/g)
IPPD (101-72-4)	96	1.13	0.66 – 24.5	–
6PPD (793-24-8)	100	309	31.4 – 831	–

Approximate instrument detection limits (IDLs) provided when applicable to detection results and are calculated as 30% of the reported instrument quantification limit (IQL) from the study.

Expected Exposure Potential of Unmonitored PPD Derivatives

DTSC is taking a class-based approach to PPD derivatives to ensure that the definition captures chemicals with structural similarities to the more-studied members of the class. DTSC may consider structurally similar chemicals with known toxicity profiles to predict the behavior of chemicals for which there is less available information (CCR 69502.2(b)(1)(D)).

The previous sections have demonstrated the fact that more-studied PPD derivatives are able to exist in a multitude of environmental media at detectable concentrations. The ubiquity of more-studied PPD derivatives indicates the exposure potential for less-studied members of the class if they are used in similar dispersive products, like tires, or in similar volumes.

4.2. Reliable Information Regarding Exposure

Reference: California Code of Regulations, Title 22, sections 69501.1(a)(57), 69501.1(a)(58), and 69502.2(b)(3)

The SCP Regulations direct the Department to consider potential exposures to the chemical based on reliable information.

The SCP Regulations instruct DTSC to consider reliable information that demonstrates the occurrence or potential occurrence of exposure to chemicals (22 CCR sections 69502.2(b)(2)). The SCP Regulations also instruct DTSC to consider the extent and quality of information that is available to substantiate potential exposures (22 CCR section 69502.2(b)(3)). In addition, DTSC adheres to CCR, Title 22, sections 69501.1(a)(57), 69501.1(a)(58), and 69503.2(b)(1)(C) to ensure that evidence regarding PPD derivative exposures meets this regulatory standard. In doing so, DTSC has determined that there is sufficient high-quality, reliable information available to demonstrate the occurrence or potential occurrence of exposures to PPD derivatives.

Reliable Information

CCR, Title 22, section 69501.1(a)(57) defines scientific studies or information as being reliable if they have been scientifically peer reviewed or published by an agency that regulates chemicals. All the information presented in this section regarding potential for exposure to PPD derivatives has

originated from either scientifically peer reviewed literature (e.g., the scientific journal *Environmental Science & Technology*) or agencies that govern chemicals (e.g., U.S. EPA). Therefore, DTSC has determined that the data supporting the potential for exposure to PPD derivatives qualify as reliable information and meet the standard set forth in the SCP Regulations.

Reliable Information Demonstrating the Occurrence or Potential Occurrence of Exposures to a Chemical

CCR, Title 22, section 69501.1(a)(58) describes data that are reliable in the context of exposure to a chemical. Example data sources include environmental monitoring, biomonitoring, and exposure or environmental modeling. All data presented in this section regarding potential for exposure to PPD derivatives are either environmental monitoring (e.g., water) or biomonitoring (e.g., human urine). Therefore, DTSC has determined that the data supporting the potential for exposure to PPD derivatives are reliable information in the context of chemical exposure and meet the standard set forth in the SCP Regulations.

Extent and Quality of Available Information

CCR, Title 22, section 69503.2(b)(1)(C) instructs DTSC to consider the quality of available information by assessing its level of rigor, degree of independent review and validation, relevancy, and author's credentials. All data presented in this section regarding potential for exposure to PPD derivatives are relevant because the reports focus on chemicals within the proposed PPD derivatives class. All monitoring studies are independently peer-reviewed and provide detailed supplemental information regarding the quality control procedures to ensure the validity of experimental methodology. When available, data have been compiled from multiple sources of research to provide the full extent of relevant information. DTSC has determined that the data supporting the potential for exposure to PPD derivatives are high quality and meet the standard set forth in the SCP Regulations.

5. POTENTIAL FOR WIDESPREAD ADVERSE IMPACTS

Reference: California Code of Regulations, Title 22, section 69502.2(b)(1)(C)

The SCP Regulations instruct the Department to give special consideration to the potential for a chemical to contribute to or cause widespread adverse impacts.

DTSC has determined that PPD derivatives meet the criteria for inclusion on the Candidate Chemicals List (CCR, Title 22, section 69502.2(b)):

(1) There are potential exposures to PPD derivatives.
(2) There is potential for one or more of these PPD derivative exposures to contribute to or cause adverse impacts.
(3) DTSC has considered the extent and quality of information that is available to substantiate the existence or absence of these potential exposures and adverse impacts.

This document demonstrates that PPD derivatives have the potential to impair the survival of wildlife, specifically of aquatic species, or to cause dermatotoxicity in people by triggering allergic contact dermatitis. As defined here, PPD derivatives are chemicals with reactive moieties that likely drive their toxic effects. Beyond the hazards of the PPD derivatives themselves, they may degrade or transform into chemicals with similar hazard traits. For example, the oxidation products of PPD are also haptens (Meyer and Fischer 2015), and one of the oxidation products of 6PPD, 6PPD-quinone, has recently been reported to have an LC_{50} of 0.041 μg/L for coho salmon hatchlings (Lo et al. 2023), ranking 6PPD-quinone among the most aquatically toxic chemicals compared to those with existing Clean Water Act Aquatic Life Ambient Water Quality Criteria (Tian et al. 2022). These problematic transformation products, some of which are flagged as persistent in the environment (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d; ToxServices, LLC 2021e), elevate DTSC's concern for PPD derivatives. The detection of PPD derivatives and their transformation products in water, soil, and even deep-sea sediment (Zeng et al. 2023) suggests that they may be somewhat persistent or that their constant release into the environment outpaces their degradation. The presence of PPD derivatives in the environment increases the likelihood of causing or contributing to toxic effects.

The hazard traits associated with PPD derivatives may pose greater concern in sensitive subpopulations. For example, workers who use or manufacture PPD derivatives are more likely to become sensitized and have subsequent exposures that trigger an allergic dermatotoxic response (Herve-Bazin et al. 1977). In addition, available information indicates that PPD derivatives are more likely to partition to organisms or sediment than to remain in the water column (ToxServices, LLC 2021a; ToxServices, LLC 2021b; ToxServices, LLC 2021c; ToxServices, LLC 2021d; ToxServices, LLC 2021e); thus, they have the potential to pose increased concern for aquatic invertebrates that readily

contact the sediment and filter particulates from the water, such as juvenile and adult mussels. Importantly, California's *threatened* or *endangered* salmonids are especially sensitive to certain transformation products of PPD derivatives (Tian et al. 2021; Tian et al. 2022; Brinkmann et al. 2022; Greer et al. 2023; Nair et al. 2023). Salmonid populations are found throughout the state, indicating the potential for widespread impacts.

Adverse aquatic impacts associated with the hazards of PPD derivatives and their transformation products have the potential to be widespread given the ways in which these chemicals are used. Some uses of PPD derivatives are dispersive, meaning the chemicals are readily released and dispersed into the environment as a result of their intended uses. For example, virtually all of the more than 171 million tires currently in service in California use at least one PPD derivative (USTMA 2021; DTSC 2022; Emissions Analytics 2022) because several PPD derivatives serve as highly effective antiozonants and antioxidants (Huntink et al. 2004). The chemicals can spread in the environment via tire wear particles. Additionally, eight PPD derivatives are considered HPV chemicals in the U.S. (Table 10), meaning they are produced or imported in high quantities and are, hence, used in high quantities. In most cases, usage data is lacking for members of the class, but because their chemistry is based on the same core moiety as other HPV PPD derivatives, they would have the potential for similar exposure patterns if they were used similarly and were produced in similar volumes.

In sum, due to the exposure potential combined with the high acute aquatic toxicity and dermatotoxicity, the large class of PPD derivatives has the potential to contribute to or cause widespread adverse impacts in California, including to sensitive subpopulations and threatened or endangered species. In making this determination, DTSC considered the extent and reliability of information to substantiate the addition of the class of PPD derivatives to the Candidate Chemicals List. Where possible, we relied on data from authoritative bodies and published papers. We also relied on the HCD, a U.S. EPA tool, intended to define structurally related chemicals. QSAR helped to fill the dearth of information on the chemical properties of this class. These tools and studies are fit for the purpose of adding to the Candidate Chemicals List. Therefore, we propose adding this class of chemicals, as defined herein, to the DTSC Candidate Chemicals List. This will enable the members of this class to be further considered within the context of specific products for potential regulatory action.

ACKNOWLEDGEMENTS

REFERENCES

16 CFR 1500.13. Title 16, Code of Federal Regulations (CFR), section 1500.13. Listing of "strong sensitizer" substances. Available at: https://www.law.cornell.edu/cfr/text/16/1500.13.

22 CCR 69502.2. (2013). Title 22, section 69502.2 of the California Code of Regulations (CCR). Candidate Chemicals Identification. Enacted: 2013. Available at: https://govt.westlaw.com/calregs/Document/IADCC5E955B6111EC9451000D3A7C4BC3?viewType=FullText&originationContext=documenttoc&transitionType=CategoryPageItem&contextData=(sc.Default).

Aeby P et al. (2009). Skin sensitization to p-phenylenediamine: the diverging roles of oxidation and n-acetylation for dendritic cell activation and the immune response. Journal of Investigative Dermatology. 129(1):99–109. doi: 10.1038/jid.2008.209.

Aldridge DC et al. (2023). Freshwater mussel conservation: a global horizon scan of emerging threats and opportunities. Global Change Biology. 29(3):575–589. doi: 10.1111/gcb.16510.

Bacharewicz-Szczerbicka J et al. (2019). Paraphenylenediamine and related chemicals as allergens responsible for allergic contact dermatitis. Archives of Medical Science: AMS. 17(3):714–723. doi: 10.5114/aoms.2019.86709.

Basketter D, Darlenski R and Fluhr JW. (2008). Skin irritation and sensitization: mechanisms and new approaches for risk assessment. Skin Pharmacology and Physiology. 21(4):191–202. doi: 10.1159/000135635.

Blair SI, Barlow CH and McIntyre JK. (2021). Acute cerebrovascular effects in juvenile coho salmon exposed to roadway runoff. Canadian Journal of Fisheries and Aquatic Sciences. doi: 10.1139/cjfas-2020-0240.

Bolton JL et al. (2000). Role of quinones in toxicology. Chemical Research in Toxicology. 13(3):135–160. doi: 10.1021/tx9902082.

Brinkmann M et al. (2022). Acute toxicity of the tire rubber-derived chemical 6PPD-quinone to four fishes of commercial, cultural, and ecological importance. Environmental Science & Technology Letters. acs.estlett.2c00050. doi: 10.1021/acs.estlett.2c00050.

California Natural Diversity Database. (2023). State and Federally Listed Endangered and Threatened Animals of California. California Department of Fish and Wildlife. Sacramento, CA.

CalRecycle. (2020). California TDP Catalog. California Department of Resources Recycling and Recovery (CalRecycle). Available at: https://www.e-productcatalog.com/TDPCatalog/. Accessed 25 Jan 2021.

Cao G et al. (2022). New evidence of rubber-derived quinones in water, air, and soil. Environmental Science & Technology. 56(7):4142–4150. doi: 10.1021/acs.est.1c07376.

Cao G. (2023). Personal communication with "New Evidence of Rubber-Derived Quinones in Water, Air, and Soil" (2022) author. Email correspondence with Guodong Cao.

CARB. (1993). The identification of federal hazardous air pollutants as toxic air contaminants. California Air Resources Board (CARB). Available at: https://ww2.arb.ca.gov/sites/default/files/classic/toxics/id/hapstacs.pdf.

CDFW. (2023). Biogeographic Information and Observation System (BIOS) tool. California Department of Fish and Wildlife (CDFW). Available at: https://apps.wildlife.ca.gov/bios6/. Accessed 17 Feb 2023.

CDFW. (2017). Historic Trout Watersheds [ds440] GIS Dataset. Biogeographic Information and Observation System (BIOS). California Department of Fish and Wildlife (CDFW). Available at: https://map.dfg.ca.gov/metadata/DS0440.html.

Chipinda I, Hettick JM and Siegel PD. (2011). Haptenation: Chemical reactivity and protein binding. Journal of Allergy. 2011:1–11. doi: 10.1155/2011/839682.

Clean Production Action. (2018). GreenScreen® for Safer Chemicals. Hazard Assessment Guidance for Chemicals, Polymers, and Products. Version 1.4. Available at: https://www.greenscreenchemicals.org/images/ee_images/uploads/resources/GreenScreen_Guidance_v1_4_2018_01_Final.pdf. Accessed 24 Feb 2023.

Cosmetic Ingredient Review. (2007). Amended Final Report of the Safety Assessment of p-Phenylenediamine, p-Phenylenediamine HCl, and p-Phenylenediamine Sulfate. Available at: https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR530.pdf.

de Zwart D et al. (2018). Aquatic exposures of chemical mixtures in urban environments: Approaches to impact assessment. Environmental Toxicology and Chemistry. 37(3):703–714. doi: 10.1002/etc.3975.

Decision C on the D and E of SCSAF to IG and I et al. (2014). Physicochemical Properties and Environmental Fate. National Academies Press (US).

Deng C et al. (2022). Distribution patterns of rubber tire-related chemicals with particle size in road and indoor parking lot dust. Science of The Total Environment. 844:157144. doi: 10.1016/j.scitotenv.2022.157144.

Deutsche Forschungsgemeinschaft. (2017). List of MAK and BAT Values 2017: Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. Report 53. John Wiley & Sons, Ltd, ISBN: 978-3-527-81212-7.

DTSC. (2022). Product-Chemical Profile for Motor Vehicle Tires Containing 6PPD - Department of Toxic Substances Control (DTSC). Available at: https://dtsc.ca.gov/wp-content/uploads/sites/31/2022/05/6PPD-in-Tires-Priority-Product-Profile_FINAL-VERSION_accessible.pdf.

DTSC. (2023). Candidate Chemicals List. Department of Toxic Substances Control (DTSC). Available at: https://calsafer.dtsc.ca.gov/cms/search/?type=Chemical. Accessed 28 Mar 2023.

DTSC. (2013). Final Statement of Reasons. Safer Consumer Products Regulations. Department of Toxic Substances Control (DTSC).

Du B et al. (2022). First report on the occurrence of *N* -(1,3-Dimethylbutyl)- *N* '-phenyl- *p* - phenylenediamine (6PPD) and 6PPD-quinone as pervasive pollutants in human urine from South China. Environmental Science & Technology Letters. 9(12):1056–1062. doi: 10.1021/acs.estlett.2c00821.

ECHA. (2023a). Table of Harmonised Entries in Annex VI to CLP. European Chemicals Agency (ECHA). Available at: https://echa.europa.eu/information-on-chemicals/annex-vi-to-clp. Accessed 6 Apr 2022.

ECHA. (2022). Para-Phenylenediamine (PPD): Brief Profile - European Chemicals Agency (ECHA). Available at: https://echa.europa.eu/brief-profile/-/briefprofile/100.003.096. Accessed 25 Aug 2022.

ECHA. (2020a). 77PD Registration Dossier: CASRN 3081-14-9. European Chemicals Agency (ECHA). Available at: https://echa.europa.eu/ro/registration-dossier/-/registered-dossier/13514/6/2/1. Accessed 28 Apr 2022.

ECHA. (2023b). IPPD Registration Dossier. European Chemicals Agency (ECHA). Available at: https://echa.europa.eu/ro/registration-dossier/-/registered-dossier/13374/6/2/1. Accessed 29 Apr 2022.

ECHA. (2021). 6PPD: 1,4-Benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl- Registration Dossier - European Chemicals Agency (ECHA). Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15367/5/1. Accessed 29 Mar 2021.

ECHA. (2020b). 7PPD Registration Dossier: CASRN 3081-01-4. European Chemicals Agency (ECHA). Available at: https://echa.europa.eu/cs/registration-dossier/-/registered-dossier/12770/1/1. Accessed 28 Apr 2022.

ECHA. (2019). 44PD (N,N'-di-sec-butyl-p-phenylenediamine) Registration Dossier, CASRN 101-96-2 for the European Chemical Agency (ECHA). Available at: https://echa.europa.eu/ro/registration-dossier/-/registered-dossier/13653/6/2/2. Accessed 24 Aug 2022.

Emissions Analytics. (2022). Fishy. Available at: https://www.emissionsanalytics.com/news/fishy. Accessed 8 Aug 2022.

French BF et al. (2022). Urban roadway runoff is lethal to juvenile coho, steelhead, and Chinook salmonids, but not congeneric sockeye. Environ Sci Technol Lett. doi: 10.1021/acs.estlett.2c00467.

Greer JB et al. (2023). Establishing an in vitro model to assess the toxicity of 6ppd-quinone and other tire wear transformation products. Environ Sci Technol Lett. doi: 10.1021/acs.estlett.3c00196.

Hermens JLM. (1990). Electrophiles and acute toxicity to fish. Environmental Health Perspectives. 219–225. doi: 10.1289/ehp.9087219.

Herve-Bazin B et al. (1977). Occupational eczema from N-isopropyl-N'-phenylparaphenylenediamine (IPPD) and N-dimethyl-1,3 butyl-N'-phenylparaphenylenediamine (DMPPD) in tyres. Contact Dermatitis. 3(1):1–15. doi: 10.1111/j.1600-0536.1977.tb03580.x.

Hiki K et al. (2021). Acute toxicity of a tire rubber-derived chemical, 6PPD quinone, to freshwater fish and crustacean species. Environmental Science & Technology Letters. 8(9):779–784. doi: 10.1021/acs.estlett.1c00453.

Hiki K and Yamamoto H. (2022). The tire-derived chemical 6PPD-quinone is lethally toxic to the white-spotted char *Salvelinus leucomaenis pluvius* but not to two other salmonid species. Environmental Science & Technology Letters. acs.estlett.2c00683. doi: 10.1021/acs.estlett.2c00683.

Hu X et al. (2022). Transformation product formation upon heterogeneous ozonation of the tire rubber antioxidant 6PPD (*N*-(1,3-dimethylbutyl)-*N*'-phenyl-*p*-phenylenediamine). Environ Sci Technol Lett. doi: 10.1021/acs.estlett.2c00187.

Hua X et al. (2022). Long-term exposure to tire-derived 6-PPD quinone causes intestinal toxicity by affecting functional state of intestinal barrier in *Caenorhabditis elegans*. Science of The Total Environment. 160591. doi: 10.1016/j.scitotenv.2022.160591.

Hua X et al. (2023). Exposure to 6-PPD quinone at environmentally relevant concentrations causes abnormal locomotion behaviors and neurodegeneration in *Caenorhabditis elegans*. Environmental Science & Technology. acs.est.2c08644. doi: 10.1021/acs.est.2c08644.

Huang W et al. (2021). Occurrence of substituted *p*-phenylenediamine antioxidants in dusts. Environmental Science & Technology Letters. 8(5):381–385. doi: 10.1021/acs.estlett.1c00148.

Hunt I. (2023). Ch12 : Substituent Effects. University of Calgary (UCalgary). Available at: http://www.chem.ucalgary.ca/courses/350/Carey5th/Ch12/ch12-8b.html. Accessed 17 Mar 2023.

Huntink NM, Datta RN and Noordermeer JWM. (2004). Addressing durability of rubber compounds. Rubber Chemistry and Technology. 77(3):476–511. doi: 10.5254/1.3547833.

IUPAC. (2014). Quaternary Ammonium Compounds. Compendium of Chemical Terminology. International Union of Pure and Applied Chemistry (IUPAC). Available at: https://goldbook.iupac.org/terms/view/Q05003. Accessed 6 Feb 2023.

IUPAC. (1996). Component. Compendium of Chemical Terminology. International Union of Pure and Applied Chemistry (IUPAC). Available at: https://goldbook.iupac.org/terms/view/C01209. Accessed 6 Feb 2023.

Jenkinson C et al. (2010). Characterization of *p*-phenylenediamine–albumin binding sites and T-cell responses to hapten-modified protein. Journal of Investigative Dermatology. 130:732–742. doi: doi:10.1038/jid.2009.271.

Johannessen C et al. (2021a). The tire wear compounds 6PPD-quinone and 1,3-diphenylguanidine in an urban watershed. Arch Environ Contam Toxicol. doi: 10.1007/s00244-021-00878-4.

Johannessen C et al. (2022). Air monitoring of tire-derived chemicals in global megacities using passive samplers. Environmental Pollution. 314:120206. doi: 10.1016/j.envpol.2022.120206.

Johannessen C, Helm P and Metcalfe CD. (2021b). Detection of selected tire wear compounds in urban receiving waters. Environmental Pollution. 287:117659. doi: 10.1016/j.envpol.2021.117659.

Johannessen C and Metcalfe CD. (2022). The occurrence of tire wear compounds and their transformation products in municipal wastewater and drinking water treatment plants. Environmental Monitoring and Assessment. 194(10):731. doi: 10.1007/s10661-022-10450-9.

Klöckner P et al. (2021). Organic markers of tire and road wear particles in sediments and soils: Transformation products of major antiozonants as promising candidates. Environmental Science & Technology. 55(17):11723–11732. doi: 10.1021/acs.est.1c02723.

Kyziol JB and Frej H. (1988). Substituent effects on physical properties of substituted azobenzenes. Chem Papers. 42(6):781–793.

Lewis D, Mama J and Hawkes J. (2013). A review of aspects of oxidative hair dye chemistry with special reference to *N*-nitrosamine formation. Materials. 6(2):517–534. doi: 10.3390/ma6020517.

Liang B et al. (2022). E-waste recycling emits large quantities of emerging aromatic amines and organophosphites: A poorly recognized source for another two classes of synthetic antioxidants. Environmental Science & Technology Letters. 9(7):625–631. doi: 10.1021/acs.estlett.2c00366.

Lo B et al. (2023). Acute toxicity of 6PPD-quinone to early life stage juvenile Chinook (*Oncorhynchus tshawytscha*) and coho (*Oncorhynchus kisutch*) salmon. Environmental Toxicology and Chemistry. 42:815–822. doi: doi: 10.1002/etc.5568.

Mahoney H et al. (2022). Exposure to the tire rubber-derived contaminant 6PPD-quinone causes mitochondrial dysfunction *in vitro*. Environmental Science & Technology Letters. acs.estlett.2c00431. doi: 10.1021/acs.estlett.2c00431.

Mansouri K et al. (2018). OPERA models for predicting physicochemical properties and environmental fate endpoints. Journal of Cheminformatics. 10:10. doi: 10.1186/s13321-018-0263-1.

Martin TM. (2017). User's Guide for WebTEST (version 1.0). Available at: https://www.epa.gov/sites/default/files/2018-08/documents/webtest_users_guide.pdf.

Martin TM. (2020). U.S. Environmental Protection Agency: User's Guide for T.E.S.T. (U.S. EPA's Toxicity Estimation Software Tool) Version 5.1.

Mayo-Bean K et al. (2017). U.S. EPA: Estimating toxicity of industrial chemicals to aquatic organisms using the EcoSAR (Ecological Structure-Activity Relationship) class program, version 2.0. United States Environmental Protection Agency (U.S. EPA).

McFadden JP et al. (2007). Allergy to hair dye. BMJ: British Medical Journal. 334(7587):220. doi: 10.1136/bmj.39042.643206.BE.

Meyer A and Fischer K. (2015). Oxidative transformation processes and products of para-phenylenediamine (PPD) and para-toluenediamine (PTD)—a review. Environmental Sciences Europe. 27(11):1–16. doi: 10.1186/s12302-015-0044-7.

Moman RN, Gupta N and Varacallo M. (2023). Physiology, Albumin. in: StatPearls. StatPearls Publishing, Treasure Island (FL).

Nair P et al. (2023). Synthesis and Toxicity Evaluation of Tire Rubber-Derived Quinones (working paper).

NCBI. (1965). Haptens - Medical Subject Headings (MeSH) from the National Center for Biotechnology Information (NCBI). Available at: https://www.ncbi.nlm.nih.gov/mesh?Db=mesh&Cmd=DetailsSearch&Term=%22Haptens%22%5BMeSH+Terms%5D. Accessed 28 Jul 2023.

NIH. (2021). GHS Classification: National Institutes of Health (NIH). Available at: https://pubchem.ncbi.nlm.nih.gov/ghs/. Accessed 28 Jul 2023.

NITE. (2023). GHS Classification Results. National Institute of Technology and Evaluation (NITE). Available at: https://www.nite.go.jp/chem/english/ghs/all_fy_e.html. Accessed 6 Apr 2023.

NTP. (2023). OPERA. Open (Quantitative) Structure-activity/property Relationship App. National Toxicology Program (NTP). Available at: https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-opera/opera.html. Accessed 24 Feb 2023.

OECD. (2004). SIDS Initial Assessment Report for N-(1,3-Dimethylbutyl)-N´-phenyl-1,4-phenylenediamine (6PPD), Organisation for Economic Co-operation and Development (OECD). Available at: https://hpvchemicals.oecd.org/UI/handler.axd?id=5e1a446c-5969-479c-9270-7ced8726952e.

OECD. (2000). SIDS Initial Assessment Report for N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD), Organisation for Economic Co-operation and Development (OECD). Available at: https://hpvchemicals.oecd.org/ui/handler.axd?id=7b63976e-35f2-4170-89cf-a202982098fa.

OSPAR Commission. (2006). Hazardous Substances Series 4-(dimethylbutylamino)diphenylamine (6PPD) 2005 (2006 Update). Available at: https://www.ospar.org/documents?v=7029.

Peiser M et al. (2012). Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects: Current knowledge assembled at an international workshop at BfR, Germany. Cellular and Molecular Life Sciences. 69(5):763–781. doi: 10.1007/s00018-011-0846-8.

Peng W et al. (2022). Exposure to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) affects the growth and development of zebrafish embryos/larvae. Ecotoxicology and Environmental Safety. 232:113221. doi: 10.1016/j.ecoenv.2022.113221.

Peter KT et al. (2020). More than a first flush: Urban creek storm hydrographs demonstrate broad contaminant pollutographs. Environmental Science & Technology. 54(10):6152–6165. doi: 10.1021/acs.est.0c00872.

Prosser RS et al. (2017a). Variation in the toxicity of sediment-associated substituted phenylamine antioxidants to an epibenthic (Hyalella azteca) and endobenthic (Tubifex tubifex) invertebrate. Chemosphere. 181:250–258. doi: 10.1016/j.chemosphere.2017.04.066.

Prosser RS et al. (2017b). Effect of substituted phenylamine antioxidants on three life stages of the freshwater mussel *Lampsilis siliquoidea*. Environmental Pollution. 229:281–289. doi: 10.1016/j.envpol.2017.05.086.

PubChem. (2022). P-Phenylenediamine: 106-50-3. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/7814. Accessed 7 Nov 2022.

PubChem. (2023). PubChem. PPD Derivative CASRNs. Available at: https://pubchem.ncbi.nlm.nih.gov/. Accessed 6 Feb 2023.

Rauert C et al. (2022). Concentrations of tire additive chemicals and tire road wear particles in an Australian urban tributary. Environmental Science & Technology. acs.est.1c07451. doi: 10.1021/acs.est.1c07451.

Rossomme E et al. (2023). Computational studies of rubber ozonation explain the effectiveness of 6PPD as an antidegradant and the mechanism of its quinone formation. Environmental Science & Technology. acs.est.2c08717. doi: 10.1021/acs.est.2c08717.

Rypel A. (2022). Losing mussel mass – the silent extinction of freshwater mussels. Available at: https://californiawaterblog.com/2022/10/09/losing-mussel-mass-the-silent-extinction-of-freshwater-mussels/. Accessed 13 Jan 2023.

Safe Work Australia. (2023). Hazardous Chemical Information System (HCIS). Available at: https://hcis.safeworkaustralia.gov.au/HazardousChemical. Accessed 23 Aug 2023.

Saifur S and Gardner CM. (2021). Loading, transport, and treatment of emerging chemical and biological contaminants of concern in stormwater. Water Science and Technology. 83(12):2863–2885. doi: 10.2166/wst.2021.187.

Santos N. (2014). PISCES: Coastal Rainbow Trout Range - FSSC [ds1282]. Califirnia Department of Fish and Wildlife. Biogeographic Information and Observation System (BIOS). Available at: https://www.arcgis.com/home/item.html?id=96afe0a18ad14e4d93049be44beca626.

Scholz NL et al. (2011). Recurrent die-offs of adult coho salmon returning to spawn in Puget Sound lowland urban streams. PLOS ONE. 6(12):e28013. doi: 10.1371/journal.pone.0028013.

Seiwert B et al. (2022). Abiotic oxidative transformation of 6-PPD and 6-PPD quinone from tires and occurrence of their products in snow from urban roads and in municipal wastewater. Water Research. 212:118122. doi: 10.1016/j.watres.2022.118122.

Smith MN, Cohen Hubal EA and Faustman EM. (2020). A case study on the utility of predictive toxicology tools in alternatives assessments for hazardous chemicals in children's consumer products. Journal of Exposure Science & Environmental Epidemiology. 30(1):160–170. doi: 10.1038/s41370-019-0165-y.

Stahl RG, Lieder PH and Hutton DG. (1990). Relationship between aquatic toxicity and oxidative degradation of unsubstituted phenylenediamines. Environmental Toxicology and Chemistry. 9(4):485–488. doi: 10.1002/etc.5620090411.

Tian Z et al. (2021). A ubiquitous tire rubber–derived chemical induces acute mortality in coho salmon. Science. 371(6525):185–189. doi: 10.1126/science.abd6951.

Tian Z et al. (2022). 6PPD-quinone: Revised toxicity assessment and quantification with a commercial standard. Environmental Science & Technology Letters. acs.estlett.1c00910. doi: 10.1021/acs.estlett.1c00910.

ToxServices, LLC. (2021a). N-Isopropyl-N'-phenyl-P-phenylenediamine (IPPD) (CAS# 101-72-4) GreenScreen® for safer chemicals (GreenScreen®) Assessment. Available at: https://www.ezview.wa.gov/Portals/_1962/Documents/6ppd/GreenScreenExecutiveSummaryForIPPD.pdf.

ToxServices, LLC. (2021b). N-(1,4-Dimethylpentyl)-N'-Phenylbenzene-1,4-Diamine (CAS# 3081-01-4) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment. Available at: https://www.ezview.wa.gov/Portals/_1962/Documents/6ppd/GreenScreenExecutiveSummaryForGS-1203.pdf.

ToxServices, LLC. (2021c). N,N'-Dicyclohexyl-4-phenylenediamine (CCPD) (CAS# 4175-38-6) GreenScreen® for safer alternatives (GreenScreen®) assessment. Available at: https://www.ezview.wa.gov/Portals/_1962/Documents/6ppd/GreenScreenExecutiveSummaryForCCPD.pdf.

ToxServices, LLC. (2021d). N-(1,3-Dimethylbutyl)-N'-Phenyl-P-Phenylenediamine (6PPD) (CAS# 793-24-8) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment. Available at: https://www.ezview.wa.gov/Portals/_1962/Documents/6ppd/GreenScreenExecutiveSummaryFor6PPD.pdf.

ToxServices, LLC. (2021e). N,N'-Bis(1,4-Dimethylpentyl)-P-Phenylenediamine (77PPD) (CAS# 3081-14-9) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment. Available at: https://www.ezview.wa.gov/Portals/_1962/Documents/6ppd/GreenScreenExecutiveSummaryFor77PPD.pdf.

Turunen M, Olsson J and Dallner G. (2004). Metabolism and function of coenzyme Q. Biochimica et Biophysica Acta (BBA) - Biomembranes. 1660(1):171–199. doi: 10.1016/j.bbamem.2003.11.012.

UCLA. (2023). Illustrated Glossary of Organic Chemistry - Substituent. Institute for Reduction of Cognitive Entropy in Organic Chemistry. University of California, Los Angeles (UCLA). Available at: http://www.chem.ucla.edu/~harding/IGOC/S/substituent.html. Accessed 10 Feb 2023.

United Nations (ed). (2021). Globally harmonized system of classification and labelling of chemicals (GHS); Ninth revised edition. United Nations, New York Geneva, ISBN: 978-92-1-117252-2.

U.S. EPA. (2023a). Hazard Comparison Dashboard (HCD) (beta - no longer active). United States Environmental Protection Agency (U.S. EPA). Available at: https://hazard.sciencedataexperts.com/#/hazard/report. Accessed 8 Nov 2022.

U.S. EPA. (2023b). Distributed Structure-Searchable Toxicity (DSSTox) Database. United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/chemical-research/distributed-structure-searchable-toxicity-dsstox-database. Accessed 16 Mar 2023.

U.S. EPA. (2023c). CompTox Chemicals Dashboard - About. United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/chemical-research/comptox-chemicals-dashboard-about.

U.S. EPA. (2015a). Initial List of Hazardous Air Pollutants with Modifications. United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/haps/initial-list-hazardous-air-pollutants-modifications. Accessed 28 Jul 2023.

U.S. EPA. (2000). Hazardous air pollutant notebook for p-phenylenediamine (106-50-3). United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/sites/default/files/2016-09/documents/p-phenylenediamine.pdf.

U.S. EPA. (2011). Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation. Version 2.0. United States Environmental Protection Agency (U.S. EPA).

U.S. EPA. (2012). Sustainable Futures / P2 Framework Manual EPA-748-B12-001. 5. Estimating Physical / Chemical and Environmental Fate Properties with EPI Suite. United States Environmental Protection Agency (U.S. EPA).

U.S. EPA. (2015b). EPI Suite™-Estimation Program Interface. United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface. Accessed 8 Mar 2023.

U.S. EPA. (2023d). CompTox Chemicals Dashboard. Batch search for PPD derivative CASRN substance identifiers for Average Mass, TEST Model Predictions, OPERA Model Predictions, Curation Level Details, and Physicochemical Property Values. United States Environmental Protection Agency (U.S. EPA). Available at: https://comptox.epa.gov/dashboard/. Accessed 4 Feb 2023.

U.S. EPA. (2015c). Recommendations for Estimating Transport Between Environmental Compartment (Fugacity) for Existing chemicals, including HPV chemicals. United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/tsca-screening-tools/recommendations-estimating-transport-between-environmental-compartment. Accessed 23 Aug 2023.

U.S. EPA. (2014). Persistent Organic Pollutants: A Global Issue, A Global Response. United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/international-cooperation/persistent-organic-pollutants-global-issue-global-response. Accessed 28 Mar 2023.

U.S. EPA. (2016). EPA EcoBox Tools by Exposure Pathways - Exposure Pathways In ERA. United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/ecobox/epa-ecobox-tools-exposure-pathways-exposure-pathways-era. Accessed 31 Jan 2023.

U.S. EPA. (2023e). High Production Volume List. PPD derivative CASRNs. CompTox Chemicals Dashboard. United States Environmental Protection Agency (U.S. EPA). Available at: https://comptox.epa.gov/dashboard/chemical-lists/EPAHPV. Accessed 23 Jan 2023.

U.S. EPA. (2023f). Chemical and Products Database (CPDat). Downloadable databases searched by PPD derivative CASRNs. United States Environmental Protection Agency (U.S. EPA). Available at: https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat. Accessed 6 Feb 2023.

U.S. EPA. (2021). CompTox Chemicals Dashboard. Available at: https://comptox.epa.gov/dashboard/. Accessed 22 Feb 2021.

U.S. FDA. (2022a). Allergens in Cosmetics. United States Food and Drug Administration (U.S. FDA). Available at: https://www.fda.gov/cosmetics/cosmetic-ingredients/allergens-cosmetics. Accessed 5 Jan 2023.

U.S. FDA. (2022b). Cosmetic Products: Temporary Tattoos, Henna/Mehndi, and "Black Henna": Fact Sheet. United States Food and Drug Administration (U.S. FDA). Available at: https://www.fda.gov/cosmetics/cosmetic-products/temporary-tattoos-hennamehndi-and-black-henna-fact-sheet. Accessed 5 Jan 2023.

U.S. FDA. (2022c). Hair Dyes. Cosmetic products section of the United States Food and Drug Administration (U.S. FDA). Available at: https://www.fda.gov/cosmetics/cosmetic-products/hair-dyes. Accessed 30 Mar 2023.

U.S. FWS. (2022). Cooperative Freshwater Mussel Culture Project. United States Fish and Wildlife Service (U.S. FWS). Available at: https://www.fws.gov/project/cooperative-freshwater-mussel-culture-project. Accessed 13 Jan 2023.

USTMA. (2021). Antioxidants and antiozonants role in manufacturing safe tires. U.S. Tire Manufacturers Association (USTMA). Available at: https://dtsc.ca.gov/wp-content/uploads/sites/31/2021/08/USTMA-DTSC-6PPD-Workshop_ADA-Compliant-7.26.2021.pdf.

Varshney S et al. (2022). Toxicological effects of 6PPD and 6PPD quinone in zebrafish larvae. Journal of Hazardous Materials. 424(C):127623. doi: 10.1016/j.jhazmat.2021.127623.

Vegosen L and Martin TM. (2020). An automated framework for compiling and integrating chemical hazard data. Clean Technologies and Environmental Policy. 22(2):441–458. doi: 10.1007/s10098-019-01795-w.

Venkatesan G et al. (2021). Development of novel alternative hair dyes to hazardous para-phenylenediamine. Journal of Hazardous Materials. 402:123712. doi: 10.1016/j.jhazmat.2020.123712.

Wang W et al. (2022). Beyond substituted *p*-Phenylenediamine antioxidants: prevalence of their quinone derivatives in $PM_{2.5}$. Environmental Science & Technology. acs.est.2c02463. doi: 10.1021/acs.est.2c02463.

Wang Y, Oxer D and Hekimi S. (2015). Mitochondrial function and lifespan of mice with controlled ubiquinone biosynthesis. Nature Communications. 6(1):6393. doi: 10.1038/ncomms7393.

Williams AJ et al. (2017). The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. Journal of Cheminformatics. 9(1):61. doi: 10.1186/s13321-017-0247-6.

Williams JD et al. (1993). Conservation status of freshwater mussels of the United States and Canada. Fisheries. 18(9):6–22. doi: 10.1577/1548-8446(1993)018<0006:CSOFMO>2.0.CO;2.

Wu J et al. (2023). A new toxicity mechanism of *N*-(1,3-Dimethylbutyl)-*N*'-phenyl-*p*-Phenylenediamine quinone: Formation of DNA adducts in mammalian cells and aqueous organisms. Science of The Total Environment. 866:161373. doi: 10.1016/j.scitotenv.2022.161373.

Wu Y, Venier M and Hites RA. (2020). Broad exposure of the North American environment to phenolic and amino antioxidants and to ultraviolet filters. Environmental Science & Technology. 54(15):9345–9355. doi: 10.1021/acs.est.0c04114.

Young A et al. (2018). Urban stormwater runoff negatively impacts lateral line development in larval zebrafish and salmon embryos. Scientific Reports. 8(1):1–14. doi: 10.1038/s41598-018-21209-z.

Zeng L et al. (2023). Widespread occurrence and transport of *p*-Phenylenediamines and their quinones in sediments across urban rivers, estuaries, coasts, and deep-sea regions. Environmental Science & Technology. acs.est.2c07652. doi: 10.1021/acs.est.2c07652.

Zhang HY et al. (2023a). Occurrence and risks of 23 tire additives and their transformation products in an urban water system. Environment International. 171:107715. doi: 10.1016/j.envint.2022.107715.

Zhang R et al. (2023b). Fates of Benzotriazoles, Benzothiazoles, and *p*-Phenylenediamines in wastewater treatment plants in Malaysia and Sri Lanka. ACS ES&T Water. acsestwater.2c00410. doi: 10.1021/acsestwater.2c00410.

Zhang Y et al. (2021a). *P*-Phenylenediamine antioxidants in $PM_{2.5}$: The underestimated urban air pollutants. Environmental Science & Technology. acs.est.1c04500. doi: 10.1021/acs.est.1c04500.

Zhang YJ et al. (2022). Widespread *N*-(1,3-Dimethylbutyl)-*N*'-phenyl-*p*-phenylenediamine quinone in size-fractioned atmospheric particles and dust of different indoor environments. Environ Sci Technol Lett. doi: 10.1021/acs.estlett.2c00193.

Zhang ZF et al. (2021b). Diphenylamine antioxidants in wastewater influent, effluent, biosolids and landfill leachate: Contribution to environmental releases. Water Research. 189:116602. doi: 10.1016/j.watres.2020.116602.

Zhao HN et al. (2023). Screening *p*-Phenylenediamine antioxidants, their transformation products, and industrial chemical additives in crumb rubber and elastomeric consumer products. Environmental Science & Technology. acs.est.2c07014. doi: 10.1021/acs.est.2c07014.

Zhong L et al. (2022). IPPD-induced growth inhibition and its mechanism in zebrafish. Ecotoxicology and Environmental Safety. 239:113614. doi: 10.1016/j.ecoenv.2022.113614.

APPENDIX A: PPD DERIVATIVE IDENTIFICATION INFORMATION

Appendix A, Table 1: PPD derivative curation descriptions (Williams et al. 2017; U.S. EPA 2023d).

Quality Control (QC) Level	Curation Description	Count
1	Expert curated: highest confidence in accuracy and consistency of unique chemical identifiers	60 (3.2%)
2	Expert curated: unique chemical identifiers confirmed using multiple public sources	13 (0.7%)
3	Programmatically curated from high quality EPA source(s). Unique chemical identifiers have no conflicts in ChemIDPlus and PubChem	5 (0.3%)
4	Programmatically curated from ChemIDPlus. Unique chemical identifiers have no conflicts in PubChem	182 (9.8%)
5	Programmatically curated from ACToR or PubChem. Unique chemical identifiers have low confidence and have a single public source	1323 (71.6%)
Unlisted	No curation level listed	266 (14.4%)
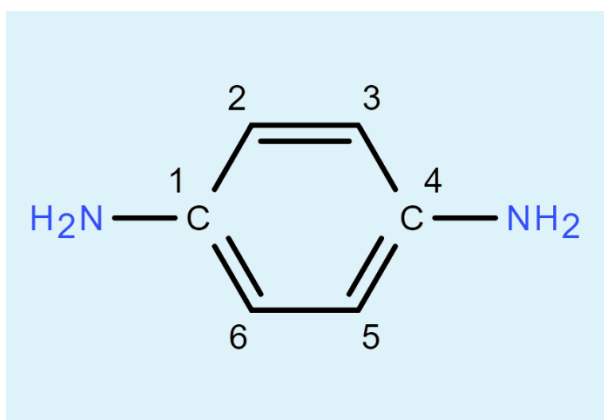
Appendix A, Figure 1: Spatial arrangement of numbered carbons in PPD's phenyl ring

| ortho-Phenylenediamine | meta-Phenylenediamine | para-Phenylenediamine |
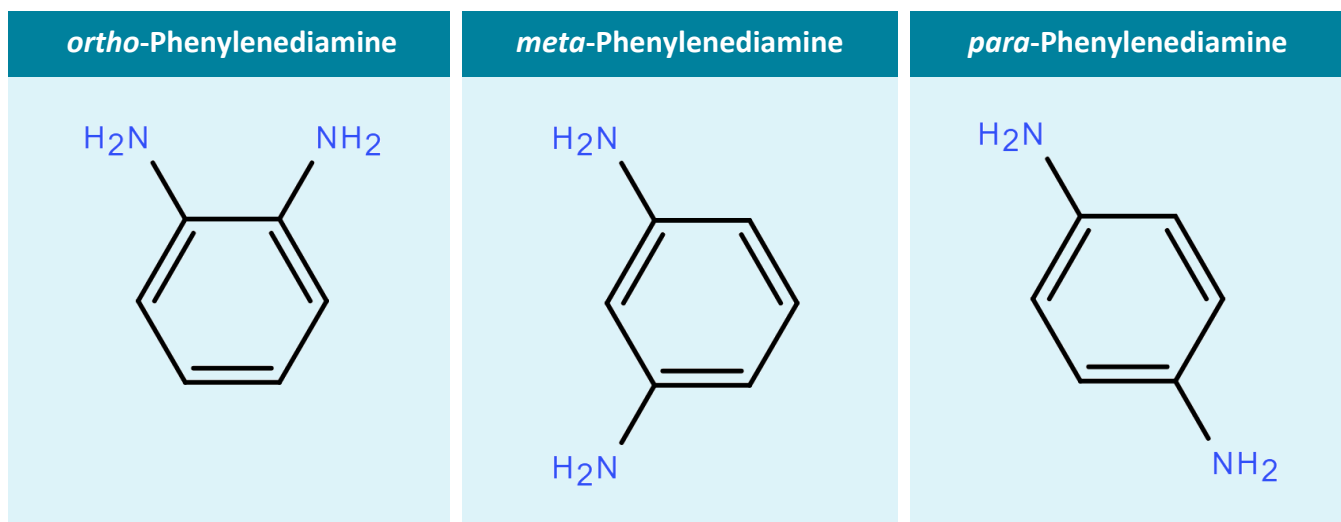
Appendix A, Figure 2: Spatial arrangement of phenyl ring substituents in ortho-, meta-, and para-phenylenediamines.

APPENDIX B: PPD DERIVATIVE WILDLIFE SURVIVAL IMPAIRMENT INFORMATION

B1. PPD

Stahl et al. (1990) compared the acute aquatic toxicity of *para-*, *ortho-*, and *meta-*phenylenediamine among three trophic levels of aquatic organisms: fish, invertebrates, and algae (*Pimephales promelas Daphnia magna*, and *Selenastrum capricornutum**, respectively). *para-*Phenylenediamine was generally the most toxic at each trophic level and, in the case of fathead minnow (*P. promelas*), had an EC_{50} more than 700 times lower (i.e., more toxic) than the ortho- and meta- isomers (Appendix B, Table 1) (Stahl et al. 1990).

Appendix B, Table 1: Acute aquatic toxicity of ortho-, meta-, and para-phenylenediamine in static tests. (Stahl et al. 1990).

Organism	EC_{50} of *ortho-*phenylenediamine (mg/L)	EC_{50} of *meta-*phenylenediamine (mg/L)	EC_{50} of *para-*phenylenediamine (PPD) (mg/L)	Test Length
P. promelas	44	1,600	**0.06**	96-hr.
D. magna	0.87	5.9	**0.28**	48-hr.
S. capricornutum*	0.16	2.4	**0.28**	96-hr.

*S. capricornutum is now known as *Raphidocelis subcapitata*.

B2. IPPD

According to the European Union (EU), IPPD merits the *very toxic to aquatic life* H400 GHS hazard statement (ECHA 2023b). Likewise, a 2021 GreenScreen® report for IPPD assigned a *very high* hazard rating for acute aquatic toxicity (ToxServices, LLC 2021a). Studies have consistently demonstrated the potent toxicity of IPPD toward multiple fish species at low concentrations. These studies derived 96-hour LC_{50} values of 0.41 mg/L for fathead minnow (*P. promelas*), 0.43 mg/L for bluegill sunfish (*Lepomis macrochirus*), and 0.34 mg/L for rainbow trout (*Oncorhynchus mykiss*) (ToxServices, LLC 2021a). The fathead minnow study was Good Laboratory Practice (GLP) compliant and followed the Organisation for Economic Co-operation and Development (OECD) Guideline 203 methodology, while compliance with these standards was not explicitly reported in the other two studies (ToxServices, LLC 2021a). The 2000 OECD Screening Information Dataset (SIDS) Initial Assessment Report described a study that identified an anomalously high 96-hour LC_{50} of 12.5 mg/L in zebrafish (*D. rerio*) (OECD 2000). In another zebrafish study, Zhong et al. tested the toxicity of IPPD on embryos from two hours until 120 hours post-fertilization, which spans the duration of embryonic development and 24 hours of juvenile stage development (Zhong et al. 2022). At 1.2 µg/L (0.0012 mg/L) the juveniles showed significantly decreased autonomous motion (Zhong et al. 2022). At higher doses, there was a decrease in hatching and body length (Zhong et al. 2022). Despite showing little change in body length, several growth factors and hormones responsible for growth and development were significantly reduced at 1.2 µg/L (Zhong et al. 2022). In response to treatment with IPPD, several molecular markers also displayed activity shifts indicative of induced oxidative stress (Zhong et al. 2022).

IPPD is acutely toxic to aquatic invertebrates and algae. The GreenScreen® report identified water flea (*D. magna*) studies that obtained 48-hour LC_{50}s of 0.98 mg/L (EU Method C.2) and 1.1 mg/L (Method EPA-660/3-75-009) (OECD 2000; ECHA 2023b). The EU Method C.2 study, which used a semi-static test, noted that IPPD had fully degraded and that the observed toxicity was due to unidentified transformation products (ECHA 2023b). This conclusion is supported by results from a separate study (EU Method C.2) that evaluated toxicity of the major IPPD hydrolysis product, 4-hydroxydiphenylamine. This study determined an EC_{50} value of 0.69 mg/L for *D. magna* based on immobilization (ECHA 2023b). With regard to phytotoxicity, two GLP compliant studies identified a 72-hour ErC_{50} (the concentration that results in a 50% reduction in growth rate) of 2.6 mg/L for the hydrolysis product and a 72-hour EbC_{50} (the concentration that results in a 50% reduction in biomass) of 26.5 mg/L for the parent IPPD in the green alga *Desmodesmus subspicatus* (ECHA 2023b).

B3. 6PPD

6PPD is already a Candidate Chemical (DTSC 2023) because it was deemed a chemical for priority action by The Convention for the Protection of the Marine Environment of the North-East Atlantic, also known as the OSPAR Convention (OSPAR Commission 2006). The OSPAR Convention is one of the authoritative bodies that SCP uses to identify Candidate Chemicals (22 CCR 69502.2 2013).

6PPD-quinone has garnered much attention recently because it is acutely lethal to coho salmon (*O. kisutch*), exceeding the GHS-established *very high* aquatic toxicity threshold by approximately 10,000 fold and is the second most toxic chemical measured in fish (Tian et al. 2022). Interestingly, some data indicate that 6PPD itself may be categorized as having *very high* aquatic toxicity for a different subset of species. For example, the LC_{50} for 6PPD in medaka [also called Japanese rice fish] (*Oryzias latipes*) is 0.028 mg/L (ECHA 2021), while Hiki et al. (2021) report zero mortality at 0.034 mg/L for 6PPD-quinone.

In addition, the chronic aquatic toxicity of 6PPD is categorized as *very high*. A 30-day test of 6PPD on early life stage medaka, using OECD test 210, demonstrated a no observed effect concentration (NOEC) of 0.0037 mg/L and lowest observed effect concentration (LOEC) of 0.011 mg/L (ECHA 2021). The LOEC is an order of magnitude below the threshold for *very high* chronic aquatic toxicity of 0.1 mg/L (U.S. EPA 2011). Varshney et al. demonstrated chronic and developmental toxicity effects in zebrafish (*Danio rerio*) (Varshney et al. 2022). While the exposed embryos survived the low doses and hatched, there was a dose-dependent reduction in eye size, swim bladder size, and heart rate in fish treated with 1 – 25 µg/L 6PPD (or 0.001 – 0.025 mg/L). The effects were not statistically significant until the higher doses 10 µg/L and 25 µg/L, but the pattern for the dose response was apparent at 1 ug/L. Similarly, Peng et al. (2022) demonstrated a reduction in hatching, autonomous movement, and body length in zebrafish embryos at 6PPD concentrations of 22 µg/L and above. These endpoints are developmental in nature but are generally indicative of less-than-healthy embryos and fry. Small changes in a fish's fitness, such as these indicators, may translate into failure to survive when resources are limited and predators abundant. In addition, the zebrafish had generally dose-responsive molecular indications of oxidative stress (Peng et al. 2022) as a potential mechanism of toxicity.

6PPD meets the criteria for *very high* toxicity to freshwater mussels (i.e., LC_{50} < 1 mg/L). Freshwater mussels represent the largest group of animals in the United States listed as *threatened* or *endangered* under the Endangered Species Act (U.S. FWS 2022). Thus, toxicity to freshwater mussels represents a major concern. Prosser et al. (2017b) tested the toxicity of 6PPD on two different species of freshwater mussel – fatmucket mussels (*Lampsilis siliquoidea)* and the generally more sensitive wavy-rayed lampmussels (*Lampsilis fasciola*)*. The 48-hour EC_{50} for the larva (called glochidia) is 439 µg/L (0.439 mg/L) for the fatmucket and 137 µg/L (0.137 mg/L) for the wavy-rayed lampmussel (Prosser et al. 2017b). The more sensitive species exceeds the GHS criteria for *very high* aquatic toxicity by nearly 10-fold. To test for chronic toxicity, juvenile fatmucket mussels were exposed in either the overlying water or through the sediment. In the 28-d exposure, the LC_{50} was 17 µg/L (0.017 mg/L) in the overlying water and 62 µg/g dry weight of sediment (Prosser et al. 2017b). After these exposures, Prosser (2017b) measured the 16-hour algal clearance rate in the surviving mussels to understand whether prior exposure to 6PPD affected the mussels' ability to eat. The EC_{50} for reduction in clearance was also 17 µg/L, the same value as the LC_{50} (Prosser et al. 2017b).

In a separate study, Prosser et al. tested the toxicity of 6PPD on amphipods (*Hyalella azteca*) that live at the sediment-water interface and sludge worms (*Tubifex tubifex*) that live within the sediment (Prosser et al. 2017a). In a 96-hour acute toxicity test, the LC_{50} for the amphipod was 250 μg/L (0.25 mg/L) in water (Prosser et al. 2017a), corresponding to a *very high* acute aquatic toxicity classification. In a 28-day test on *Hyalella,* mortality was the most sensitive endpoint, where the LC_{50} was 13 μg/L (0.013 mg/L) in water and 135 μg/g dry weight of sediment (Prosser et al. 2017a). Reproduction in *Tubifex* was the most sensitive chronic toxicity endpoint. At 4 μg/g dry weight sediment, the number of juveniles of any size was reduced by 50% (Prosser et al. 2017a). The primary route of *Tubifex* exposure is likely through the sediment and pore water. Collectively, these data indicate that 6PPD has *very high* toxicity to benthic aquatic invertebrates.

B4.   7PPD

7PPD is similar to 6PPD in structure and aquatic hazard profile. The two chemicals differ in that the alkyl side chain of 7PPD comprises seven carbons rather than six (Table 1). 7PPD carries the GHS hazard statements H400 (very toxic to aquatic life) and H410 (very toxic to aquatic life with long lasting effects) (ECHA 2020b). A 2021 ToxServices GreenScreen® report for 7PPD assigned a hazard rating of *very high* for acute aquatic toxicity across all three trophic levels (ToxServices, LLC 2021b).

7PPD is acutely toxic to fish. The studies described in the GreenScreen® report included those that were compliant with U.S. EPA GLP standards and followed U.S. EPA guidelines (Method EPA-660/3-75-009) (ToxServices, LLC 2021b). Studies on acute toxicity identified 96-hour LC_{50} values of 0.3 mg/L for bluegill sunfish (*L. macrochirus*) and 0.4 mg/L for rainbow trout (*O. mykiss*) (ECHA 2020b). A second guideline study using rainbow trout supported the initial finding and identified a 96-hour LC_{50} of 0.42 mg/L (ECHA 2020b). The GreenScreen® report also provided two separate 96-hour LC_{50} values of 1.10 and 0.06 mg/L for fathead minnow (*P. promelas*), which correspond to GHS hazard classifications of *high* and *very high*, respectively (ToxServices, LLC 2021b).

7PPD is acutely toxic to aquatic invertebrates and plants. The GreenScreen® report provided a 48-hour LC_{50} of 0.2 mg/L for the water flea (*D. magna*), based on a study in compliance with guidelines and GLP, and a 96-hour EC_{50} of 0.7 mg/L for a green microalga (*Pseudokirchneriella subcapitata*; now called *Raphidocelis subcapitata*), based on decreased biomass and growth rate (ECHA 2020b; ToxServices, LLC 2021b).

7PPD may be a chronic aquatic toxicant. The GreenScreen® report indicated a *very high* hazard rating for chronic aquatic toxicity of 7PPD, although this determination was inferred through a read-across of studies with surrogate chemicals rather than 7PPD (ToxServices, LLC 2021b).

B5. 44PD

44PD has two identical alkyl groups flanking the central phenylenediamine. It is classified as having *very high* acute aquatic toxicity to fish. The ECHA dossier includes four acute fish-toxicity studies. All the studies are GLP compliant (ECHA 2019). Rainbow trout (*O.mykiss*) and fathead minnow (*P. promelas*) both had the same LC_{50}, 0.13 mg/L (ECHA 2019) in the 96-hour assays. Similar levels of toxicity were seen in bluegill (*L. macrochirus*) LC_{50}, 0.18 mg/L, and medaka (*O. latipes*) LC_{50}, 0.37 mg/L (ECHA 2019). Chronic studies were only available for surrogate chemicals in the dossier.

44PD has *very high* acute toxicity to aquatic invertebrates. The ECHA dossier includes short term toxicity studies on the water flea (*D. magna*). The primary EC_{50} was reported as 0.54 mg/L from a 48-hour immobilization study that was GLP compliant and reliable without exception (ECHA 2019). Another supporting study reported an EC_{50} of 1.4 mg/L.

44PD is categorized as having *very high* toxicity to algae. An EC_{50} of 0.94 mg/L is reported for *Raphidocelis subcapitata* (previous names: *Pseudokirchneriella subcapitata*, *Selenastrum capricornutum*) in a 72-hour algal growth inhibition test (ECHA 2019). The test was conducted under GLP conditions and was accepted without restriction (ECHA 2019).

B6. 77PD

ECHA lists 77PD with the GHS hazard statements of H400 (very toxic to aquatic life) and H410 (very toxic to aquatic life with long lasting effects) (ECHA 2020b). A 2021 ToxServices GreenScreen® report for 77PD assigned a hazard rating of *very high* for acute and chronic aquatic toxicity (ToxServices, LLC 2021e).

77PD is acutely toxic to fish based on two studies of fathead minnow (*P. promelas*). A GLP-compliant study following OECD Guideline 204 determined a 96-hour LC_{50} of 0.14 mg/L, while a separate study (methodology and GLP compliance not specified) determined a 96-hour LC_{50} of 0.06 mg/L (ECHA 2020a). 77PD is also toxic to fathead minnows at lower concentrations under a prolonged exposure period. One study, which did not specify an experimental guideline or GLP compliance, determined a 14-day LC_{50} of 0.05 mg/L (ECHA 2020a). A GLP-compliant study following OECD Guideline 204 determined a 14-day LC_{50} of 0.067 mg/L (ECHA 2020a).

77PD is also acutely toxic to aquatic invertebrates, with 48-hour LC_{50} values of 1.7 mg/L for larvae of the midge (*Paratanytarsus parthenogenetica*) and 0.37 mg/L for the water flea (*D. magna*) (ECHA 2020a). Both studies were GLP compliant and followed U.S. EPA Method EPA660/3-75-009. No aquatic plant studies were identified in the 2021 GreenScreen® report (ToxServices, LLC 2021e).

APPENDIX C: REPORT PREPARATION

Preparers and Contributors

Simona Bălan, Ph.D. – Supervisor, External Communications and Environmental Justice Unit – Safer Consumer Products Program

Topher Buck, M.F.S. – Supervisor, Data Science, Analysis, and Interpretation Unit – Safer Consumer Products Program

Michael Garland, Ph.D. – Staff Toxicologist (Specialist) – Human and Ecological Risk Office

Kelly Grant, Ph.D. – Senior Environmental Scientist (Specialist) – Safer Consumer Products Program

Logan Hayes, M.S. – Environmental Scientist – Safer Consumer Products Program

Tiglath Moradkhan, M.S. – Environmental Scientist – Safer Consumer Products Program

Alicia Taylor, Ph.D. – Staff Toxicologist (Specialist) – Human and Ecological Risk Office

Lynn Nakayama Wong, Ph.D. – Staff Toxicologist (Specialist) – Safer Consumer Products Program

Reviewers

André Algazi – Branch Chief, Chemical and Product Evaluation Team Branch – Safer Consumer Products Program

Anne Cooper Doherty, Ph.D. – Supervisor, Chemical Evaluation Unit – Safer Consumer Products Program

Karl Palmer – Deputy Director – Safer Consumer Products Program