p-PHENYLENEDIAMINE

(CAS #106-50-3)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: April 5, 2024

Expiration Date: April 5, 2029

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GreenScreen® Executive Summary for *p*-Phenylenediamine (CAS #106-50-3)

p-Phenylenediamine (PPD) is an aromatic amine in which two amine groups are bound to a benzene ring at the carbon 1 and 4 positions, also known as the para (*p*-) positions. It functions as a dye intermediate and dye in hair dyes and dyes used in the textile industry including for the dyeing of furs. Additionally, PPD functions as a photographic developing agent, a vulcanization accelerator and antioxidant in the production of rubber compounds, a component in gasoline antioxidants, and a chemical intermediate across numerous industries including in the manufacturing of azo dyes, aramid fibers, N,N'-disubstituted PPDs, and diisocyanates for polyurethane.

In the European Union (EU), PPD is restricted when used as a hair dye substance in oxidative hair products and PPD and its salts are restricted for use in products intended for coloring eyelashes for professional use only after mixing under oxidative conditions, with a maximum concentration of 2% (free base). In the United States, PPD is a member of the hair dyeing agents commonly known as "coal tar hair dyes" regulated under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Historically, coal tar hair dyes were derived through coal mining; currently, these ingredients are petroleum-derived. In the United States, the Food and Drug Administration (U.S. FDA) has established specific requirements for the use of coal tar hair dye products. The product label must include the following warning language, and adequate directions for the recommended skin test must be provided.

"Caution - This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness (FD&C Act, 601(a))."

Additionally, the U.S. FDA has determined that the use of PPD as anything other than a hair dye is unapproved. For instance, coal-tar hair dyes are not approved for staining the skin and/or for use in temporary tattoo inks such as "black henna".

PPD is a non-flammable, non-volatile, white to light purple crystalline solid that turns purple to black when oxidized, and is soluble in water.

PPD was assigned a **GreenScreen Benchmark™ Score of 2** ("use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2c
    - High persistence-P + Moderate Group I Human Health (carcinogenicity-C, reproductive toxicity-R, developmental toxicity-D, and endocrine activity-E)
    - High P + Moderate Group II* Human Health (respiratory sensitization-SnR*)
    - High P + Moderate Group II Human Health (skin irritation-IrS)
    - High P + High Group II* Human Toxicity (repeated dose systemic toxicity-STr* and skin sensitization-SnS*)
    - High P + High Group II Human Toxicity (acute toxicity-AT and eye irritation-IrE)
    - High P + Very High Group II Human Toxicity (single dose systemic toxicity-STs and single dose neurotoxicity-Ns)
    - High P + Very High Ecotoxicity (acute aquatic toxicity-AA, and chronic aquatic toxicity-CA)
- Benchmark 2e
    - Moderate Group I Human Toxicity (C, R, D, and E)
- Benchmark 2f

- High Group II* Human Toxicity (STr* and SnS*)
- Very High Group II Human Toxicity (STs and Ns)
- Very High Ecotoxicity (AA and CA)

A data gap (DG) exists for repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), PPD meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if PPD were assigned a High score for the data gap Nr*, it would still be categorized as a Benchmark 2 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for respiratory sensitization, persistence, and bioaccumulation, and *in vitro* testing for genotoxicity and endocrine activity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

Type I (input data) uncertainties in PPD's NAMs dataset include no or insufficient experimental data for endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. PPD's Type II (extrapolation output) uncertainties include lack of defined applicability domains OECD QSAR Toolbox in examination of structural alerts, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in vitro* receptor binding activity assays, the limitation of the OECD Guideline 439 *in vitro* skin irritation assay in identifying GHS Category 3 mild skin irritants, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of PPD's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for PPD

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
M	**L**	*M*	*M*	*M*	**H**	*vH*	**H**	*vH*	DG	**H**	*M*	*M*	**H**	**vH**	**vH**	*H*	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for p-Phenylenediamine (PPD) (CAS #106-50-3)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Deb Remeikas, M.A.
Title: Toxicologist
Organization: ToxServices LLC
Date: February 11, 2024; March 20, 2024

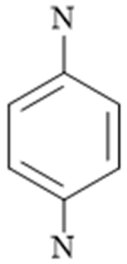
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: March 18, 2024, April 5, 2024

Expiration Date: April 5, 2029[2]

Chemical Name: *p*-Phenylenediamine (PPD)

CAS Number: 106-50-3

Chemical Structure(s) (PubChem 2024a)**:**

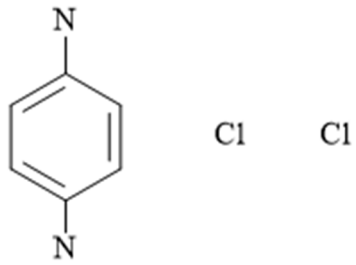


Also called: 1,4-Benzenediamine; 1,4-Diaminobenzene; 1,4-Phenylenediamine; Benzene-1,4-diamine; C.I. 76060; C.I. 76076 (Salt/Mix); C.I. Developer 13; C.I. Oxidation Base 10; p-Aminoaniline; para-Diaminobenzene; p-Benzenediamine; p-Diaminobenzene; p-Phenylenediamine (PubChem 2024a). PPDA (ECHA 2024a). Trade names: Aminogen II; AMY40784; BASF ursol D; Benzofur D; Black for Fur D; Developer PF; Durafur Black R; EC 203-404-7; ELF Color; EN300-19064; Fouramine D; Fourrine 1; Fourrine D; FOURRINE I; Fur Black 41866; Fur Black 41867; FUR BLACK R; FUR Brown 41866; Fur Yellow; Furro D; Futramine D; MAKO H; Nako H; Orsin; Oxidation base 10; P0170; Pelagol D; Pelagol DR; Pelagol Grey D; Peltol D; p-phenylenediamine base; p-PhenylenediaMine(p-PDA); p-Phenylenediamine, >=99.0% (GC/NT); p-Phenylenediamine, flakes, >=99.5%; p-Phenylenediamine, technical, >=97.0% (GC/NT); p-Phenylenediamine, zone-refined, purified by sublimation, >=99%; Q415024; Renal PF; Rodol D; Santoflex IC; Santoflex LC; STR01091; Tertral D; Ursol D; Zoba Black D (PubChem 2024a). PPDA 99.5% OR (ECHA 2024a).

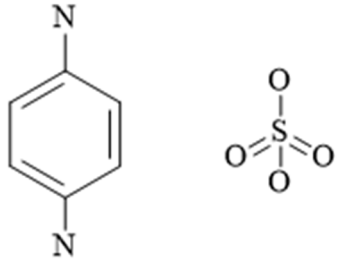
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Data for PPD were not identified for all endpoints. Therefore, *p*-phenylenediamine HCl (CAS #624-18-0) and *p*-phenylenediamine sulfate (CAS #16245-77-5 / 50994-40-6) were used as surrogates to evaluate the toxicity of PPD. Both *p*-phenylenediamine HCl and *p*-phenylenediamine sulfate are salt forms of

[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

the target chemical, they have been evaluated by the U.S. Environmental Protection Agency (U.S. EPA), Cosmetic Ingredient Review (CIR) Expert Panel, the Scientific Committee on Consumer Safety/Products (SCCS/SCCP), Australian Industrial Chemicals Introduction Scheme (AICIS) as a group with PPD (U.S. EPA 2016, CIR 2023, SCCP 2006, SCCS 2012, AICIS 2014), and they are used for read-across in the REACH dossier for PPD (ECHA 2024a).



Surrogate #1: *p*-Phenylenediamine HCl (CAS #624-18-0) (PubChem 2024b)



Surrogate #2: *p*-Phenylenediamine Sulfate (CAS #16245-77-5 / 50994-40-6) (PubChem 2024c)

Identify Applications/Functional Uses (CIR 2023, EC 2024, PubChem 2024a)**:**
1. Dye in hair dye formulations with a maximum concentration of up to 2%,
2. Dye and dye intermediate in textiles,
3. Chemical intermediate,
4. Photographic developing agent,
5. Vulcanization accelerator,
6. Antioxidant.

Known Impurities[3]:
The Cosmetic Ingredient Review (CIR) Expert Panel noted that 4-aminobiphenyl (a known urinary bladder carcinogen, LT-1) and 2-aminobiphenyl (a carcinogenic compound that induces hemangiosarcomas, LT-P1) have been found in batches of research-grade PPD (97% purity), presumably as a by-product of synthesis via reduction of p-nitroaniline (CIR 2007). The major U.S. manufacturers of PPD produce it at a purity of > 99% for use in hair dyes via the process of direct nitration of benzene without chlorinating, which does not yield aminobiphenyl compounds. The common impurities in PPD (with specification limits) include *o*-aminophenol (< 500 ppm, LT-UNK), *o*-PPD (< 200 ppm, LT-1), *m*-PPD (< 200 ppm, LT-1), and aniline (< 50 ppm, LT-1). Additionally, heavy metal content occurs at < 5 ppm for mercury, arsenic, and antimony, < 10 ppm for cadmium, and < 20 ppm for lead (CIR 2023). The CIR Expert Panel expects that 99% pure PPD is being used by the cosmetics industry (CIR 2007, 2023). Impurities above 100 ppm are evaluated individually and

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.

separately according to the GreenScreen® criteria (CPA 2018b). The current screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for PPD[4,5 6,7]: PPD was assigned a **GreenScreen Benchmark™ Score of 2** ("use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2c
  - High persistence-P + Moderate Group I Human Health (carcinogenicity-C, reproductive toxicity-R, developmental toxicity-D, and endocrine activity-E)
  - High P + Moderate Group II* Human Health (respiratory sensitization-SnR*)
  - High P + Moderate Group II Human Health (skin irritation-IrS)
  - High P + High Group II* Human Toxicity (repeated dose systemic toxicity-STr* and skin sensitization-SnS*)
  - High P + High Group II Human Toxicity (acute toxicity-AT and eye irritation-IrE)
  - High P + Very High Group II Human Toxicity (single dose systemic toxicity-STs and single dose neurotoxicity-Ns)
  - High P + Very High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA)
- Benchmark 2e
  - Moderate Group I Human Toxicity (C, R, D, and E)
- Benchmark 2f
  - High Group II* Human Toxicity (STr* and SnS*)
  - Very High Group II Human Toxicity (STs and Ns)
  - Very High Ecotoxicity (AA and CA)

A data gap (DG) exists for repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), PPD meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if PPD were assigned a High score for the data gap Nr*, it would still be categorized as a Benchmark 2 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for PPD

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
M	**L**	*M*	*M*	*M*	**H**	*vH*	**H**	*vH*	DG	**H**	*M*	*M*	**H**	**vH**	**vH**	*H*	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four

[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

Because PPD is not readily or inherently biodegradable, biodegradation is not the primary route of degradation for PPD. However, PPD rapidly degraded in water via direct and indirect photolysis in an EPA OTS 795.70 indirect photolysis screening test, and is expected to undergo direct photolysis in the air based on absorption in the UV range and QSAR modeling (ECHA 2024a, HSDB 2019). However, no phototransformation products have been identified. No hydrolysis products were predicted by OECD QSAR Toolbox under acidic, basic, and neutral conditions (OECD 2023).

Introduction

PPD is an aromatic amine in which two amine groups are bound to a benzene ring at the carbon 1 and 4 positions, also known as the para (*p*-) positions. PPD is manufactured via the reduction of *p*-nitroaniline in the presence of iron and hydrochloric acid (Ashford 2011, PubChem 2024a), and via the hydrogenation of *p*-phenylazoaniline (Ashford 2011).

In the European Union (EU), PPD is restricted when used as a hair dye substance in oxidative hair products and PPD and its salts are restricted for use in products intended for coloring eyelashes for professional use only after mixing under oxidative conditions, with a maximum concentration of 2% (free base) (CIR 2023). In the United States, PPD is a member of hair dyeing agents commonly known as "coal tar hair dyes" regulated under the Federal Food, Drug, and Cosmetic Act (FD&C Act) (CIR 2023, U.S. FDA 2024). Historically, coal tar hair dyes were derived through coal mining; currently, these ingredients are petroleum-derived. In the United States, the Food and Drug Administration (U.S. FDA) has established specific requirements for the use of coal tar hair dye products. The product label must include the following warning language, and adequate directions for the recommended skin test must be provided (U.S. FDA 2024).

Caution - This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness (FD&C Act, 601(a)).

Additionally, the U.S. FDA has determined that the use of PPD as anything other than a hair dye is unapproved. For instance, coal-tar hair dyes are not approved for staining the skin and/or for use in temporary tattoo inks such as "black henna" (U.S. FDA 2024).

ToxServices assessed PPD against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2024a). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

PPD is not listed on the SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2024) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for PPD can be found in Appendix C.

- PPD is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- PPD is listed on the U.S. DOT list as a Hazard Class Division 6.1 chemical, UN #1673, Packing Group III.
- PPD is on the following lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - EU – GHS (H-statements) Annex 6 Table 3-1 – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS New Zealand – Hazardous to the aquatic environment – Chronic Category 1.
    - GHS Australia – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS Malaysia – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS – Korea – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS Japan – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - German FEA - Substances Hazardous to Waters - Class 3 - Severe Hazard to Waters

Hazard Statement and Occupational Control

Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements that are harmonized across EU were identified for PPD, as indicated in Table 1. General personal protective equipment (PPE) recommendations and occupational exposure limits (OELs) are presented in Table 2, below.

Table 1: GHS H Statements for PPD (CAS #106-50-3) (ECHA 2024b)

H Statement	H Statement Details
H301	Toxic if swallowed.
H311	Toxic in contact with skin.
H317	May cause an allergic skin reaction.
H319	May cause serious eye irritation.
H331	Toxic if inhaled.
H400	Very toxic to aquatic life.
H410	Very toxic to aquatic life with long lasting effects.

[8] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for PPD (CAS #106-50-3)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Protective gloves and clothing. Wear safety spectacles, face shield or eye protection in combination with breathing protection.	ILO 1997	OSHA PEL*: 8h TWA: 0.1 mg/m^3 NIOSH REL*: up to 10h TWA: 0.1 mg/m^3 ACGIH TLV*: 8h TWA: 0.1 mg/m^3 [1998] CAL/OSHA PEL*: 8h TWA: 0.1 mg/m^3 IDLH: 25 mg/m^3 *skin notation for all 4 OELs.	OSHA 2021
Avoid generation and inhalation of dusts in all circumstances. Avoid substance contact. Work under a hood.	Sigma Aldrich 2023	MAK (inhalable fraction): 0.1 mg/m^3	ILO 1997

ACGIH: American Conference of Governmental Industrial Hygienists
CAL/OSHA: California Occupational Safety and Health Administration
IDLH: Immediately Dangerous to Life or Health
MAK: Maximum Workplace Concentration
NIOSH: National Institute for Occupational Safety and Health
OEL: Occupational Exposure Limit
OSHA: Occupational Safety and Health Administration
PEL: Permissible Exposure Limit
REL: Recommended Exposure Limits
STEL: Short-term Exposure Limit
TLV: Threshold Limit Value
TWA: Time Weighted Average

Physicochemical Properties of PPD

PPD is a white to purple, crystalline solid under standard temperature and pressure that turns purple to black when oxidized. It has a very low vapor pressure (7.80 x 10^{-5} mmHg), indicating it is unlikely to volatize. PPD is very soluble in water (31,000 mg/L). Its log K_{ow} indicates that it is not likely to undergo bioaccumulation.

Table 3: Physical and Chemical Properties of PPD (CAS #106-50-3)		
Property	**Value**	**Reference**
Molecular formula	$C_6H_8N_2$	PubChem 2024a
SMILES Notation	C1=CC(=CC=C1N)N	PubChem 2024a
Molecular weight	108.14 g/mol	PubChem 2024a
Physical state	Solid crystalline, flakes	ECHA 2024a, PubChem 2024a
Appearance	White to purple that turns purple to black when oxidized	PubChem 2024a
Melting point	142°C (OECD Guideline 102)	ECHA 2024a
Boiling point	274°C (ASTM Method D 1120)	ECHA 2024a

Table 3: Physical and Chemical Properties of PPD (CAS #106-50-3)		
Property	**Value**	**Reference**
Vapor pressure	$1.04x10^{-2}$ Pa (equiv. to $7.80x10^{-5}$ mmHg) at 20±1°C (OECD Guideline 104/EPA OPPTS 830.7950)	ECHA 2024a
Water solubility	31,000 mg/L at 20°C (OECD Guideline 105)	ECHA 2024a
Dissociation constant	pKa = 6.22 (calculated)	ECHA 2024a
Density/specific gravity	Bulk density = 0.726 g/mL (ASTM E-727)	ECHA 2024a
Partition coefficient	Log K_{ow} = -0.84 at 20°C (OECD Guideline 107)	ECHA 2024a
Particle size	0.4% of particles are < 20 µm (exp)	ECHA 2024a
Structure	Crystalline	PubChem 2024a
Bioavailability	Yes, systemic distribution and bioavailability confirmed (see Toxicokinetics section)	ECHA 2024, AICIS 2014

Toxicokinetics

- *Absorption*: Although no direct data were identified for absorption via the inhalation route of exposure, the toxicokinetics of PPD has been adequately studied via the oral and dermal routes of exposure. Data in rats and mice indicate that PPD is rapidly and almost entirely absorbed via the oral route of exposure. Human data indicates PPD is absorbed via the dermal route of exposure in formulations containing up to 2% PPD with the highest mean plasma concentration of 132.5 mg/L.
    - *In vitro:* In two *in vitro* toxicokinetic studies, a hair dye containing an unknown concentration of radioactive [14C]PPD was applied to a human skin and a guinea pig ear skin model for 30 minutes, and the total absorbed amount of [14C]PPD was 2.4% and 3.4%, respectively, after 24 hours (Klimisch 2, reliable with restrictions) (ECHA 2024a).
    - *Oral:* In a toxicokinetics study, Sprague Dawley rats received a single oral dose of 4 or 6.45 mg/kg PPD, and PPD was rapidly and almost entirely absorbed in the gastrointestinal tract (AICIS 2014, CIR 2023, ECHA 2024a).
    - *Oral: Surrogate: PPD HCl (CAS #624-18-0):* PPD HCl was rapidly and nearly completely absorbed after oral exposure in mice and rats (U.S. EPA 2016).
    - *Dermal:* In a toxicokinetic clinical study, subjects (28 males and 4 females) received dermal applications of dyes containing 1 and 2% PPD. The mean plasma concentrations were determined to be 97.4 and 132.5 ng/mL, respectively, and the mean area under the curve (AUC) values from zero to infinity were 966 and 1,415 ng eq PPD/mL-hr (U.S. EPA 2016).
    - *Dermal:* In another toxicokinetic clinical study, male subjects (n=8) received topical applications to the scalp of a dark-shade oxidative hair dye containing radiolabeled [14C]-PPD in which the hair, wash water, and material used in the study were measured for radioactivity in addition to blood, urine, and feces up to 120 hours post-application. The mean plasma concentration was 0.087 µg eq/mL [14C]PPD equivalent in plasma, the Tmax was 2 hours, and the mean area under the curve (AUC) value was 0.67 µg eq h/mL PPD for the time period of 0 to 12 hours (Klimisch 2, reliable with restrictions) (ECHA 2024a).
    - *Dermal:* When a hair dye formulation of 2% PPD with hydrogen peroxide was applied to the human scalp (n = 8 males), 0.54% of the applied dose was absorbed and calculated based on the excretion rate in rats (AICIS 2014, CIR 2023, ECHA 2024a, SCCS 2012).

- *Distribution:* PPD is rapidly and widely distributed throughout the body. The surrogate PPD HCl will dissociate to PPD *in situ* (ECHA 2024a), and distribute to major organs in proportion to their volume.
    - *Intraperitoneal:* In a toxicokinetic study conducted in a manner similar to OECD Guideline 117 with male rats exposed to a single intraperitoneal dose of 10 mg/kg radioactive PPD in 20 mL of Tween 20: 1.15% saline (20:80 v/v) for 72 hours, PPD was detected in internal organs, tissues, and blood (3.3%) (Klimisch 2, reliable with restrictions) (ECHA 2024a).
    - *Oral: Surrogate: PPD HCl (CAS #624-18-0):* In mice and rats, surrogate PPD HCl was distributed to major organs (i.e., blood, liver, kidney, skin, and muscle) in proportion to their volume while adipose tissue contained less PPD than predicted by its volume (U.S. EPA 2016).
- *Metabolism:* Identical in both animals and humans, PPD is predominantly metabolized to N,N'-diacetylated-p-phenylenediamine (N,N'-diacetyl-PPD). The predominantly the metabolite N,N'-diacetyl-PPD was found in the urine and feces of humans, indicating that N-acetylation is important in the inactivation of PPD in human skin (SCCS 2012).
    - *Intraperitoneal:* In the previously described toxicokinetic study conducted in a manner similar to OECD Guideline 117 with male rats, two metabolites were identified, and the major metabolite co-chromatographed with the N,N'-diacetyl-PPD standard (Klimisch 2, reliable with restrictions) (ECHA 2024a).
    - *Dermal:* In the previously described study in which a hair dye formulation of 2% PPD with hydrogen peroxide was applied to the human scalp, the two metabolites identified were N-acetyl-PPD and N,N'-diacetyl-PPD (AICIS 2014, CIR 2023, ECHA 2024a, SCCS 2012).
- *Excretion:* Toxicokinetic studies in animals and humans found that PPD is rapidly eliminated and excreted via the urine and feces.
    - *Intraperitoneal:* In the previously described toxicokinetic study conducted in a manner similar to OECD Guideline 117 with male rats, approximately 50% and 35% of the dose was excreted in the urine and feces, respectively (Klimisch 2, reliable with restrictions) (ECHA 2024a).
    - *Oral: Surrogate: PPD HCl (CAS #624-18-0):* In mice and rats, surrogate PPD HCl was excreted mostly to the urine (62-87%) the remaining in the feces with approximately 90% excretion occurring within 24 hours of dosing (U.S. EPA 2016).
    - *Dermal:* In another toxicokinetic clinical study in which subjects (28 males and 4 females) received dermal applications of dyes containing 1 and 2% PPD, the total urinary excretion was 0.72 and 0.88% of the applied test substance, respectively, with 0.04% excreted in feces and the mean elimination half-life was 7.8 hours (CIR 2023, SCCS 2012, U.S. EPA 2016).

Summary: Overall, limited data were available on the toxicokinetics of PPD via the inhalation route; however, sufficient evidence in animals exposed to oral doses of PPD and surrogate PPD HCl found rapid and complete absorption in the gastrointestinal tract, and human data indicates rapid absorption via the dermal route of exposure. PPD is distributed rapidly and widely throughout the body, and metabolized predominantly to N,N'-diacetyl-PPD with up to 62-87% excreted in urine and the remaining in feces.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): M

PPD was assigned a score of Moderate for carcinogenicity based on listing by MAK as a Group 3B Carcinogen due to limited evidence of carcinogenicity of PPD with co-exposure with hydrogen peroxide, which are commonly found together in hair dying formulations. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited or marginal evidence of carcinogenicity in animals and when they are listed by MAK as Carcinogen Group 3B (CPA 2018b). The confidence in the score is high as it is based on an authoritative A list.

- Authoritative and Screening Lists
  - *Authoritative:*
    - MAK – Carcinogen Group 3B – Evidence of carcinogenic effects but not sufficient for classification.
    - IARC – Group 3 – Agent is not classifiable as to its carcinogenicity to humans.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2024a (The authors of the ECHA dossier identified additional studies for carcinogenicity; however, only the Key study was included due to its higher reliability and adequacy in evaluating this endpoint.)
  - *Dermal*: In a non-GLP compliant chronic toxicity and carcinogenicity study, female Swiss mice (50/group) were administered topical applications 0, 5, or 10% PPD (purity unspecified) in 0.2 mL acetone, 2 times a week for 135 weeks. The animals were evaluated for mortality, clinical signs of toxicity, body weight, food consumption, gross pathology, and histopathology. No evidence of any treatment-related tumors was reported under the test conditions and study authors concluded that PPD was not carcinogenic (Klimisch 2, reliable with restrictions).
- ECHA 2024a, U.S. EPA 2016
  - *Oral*: Negative results in oral chronic toxicity/carcinogenicity studies were reported by the authors of the ECHA dossier, CIR (2023), U.S. EPA (2016), and SCCS (2012) for PPD and surrogate PPD HCl. Although there was no significant increase in the incidence of any tumor type, these were non-guideline studies and U.S. EPA (2016) noted that the reliability of these studies (Imaida et al 1983, NCI 1979) in rats and in mice (NCI 1979) were limited by poor reporting (i.e., limited information of experimental design, no specific information on organs evaluations for histopathology, inadequate reported of relative organ-weight data), the small number of control animals (i.e., 24-25/sex), low survival in all groups to termination (i.e., between 1 and 32 animals/sex/dose), failure to achieve maximum tolerated dose and/or limited reporting of study details.
- SCCNFP 1999, SCCP 2006, AICIS 2014
  - *Dermal:* In a long-term topical study, female mice and female rabbits (50/group) received topical applications of 5% or 10% PPD (purity unspecified) in 0.02 mL acetone to the shaved, intact skin, twice a week until spontaneous death occurred. No significant increase in tumors were found in mice when compared to controls and in rabbits no neoplasms were reported after 85 weeks of treatment.
- SCCP 2006, SCCS 2012
  - PPD alone was not carcinogenic to rats or mice, while in combination with hydrogen peroxide, it was potentially carcinogenic to rats.
- MAK 2000

  - Classification of PPD as a Group 3B carcinogen is based on evidence on induced tumors at the injection site after subcutaneous injection of PPD alone and in the mammary gland, uterus, and soft tissues of rats after topical and subcutaneous injection of hair dying mixtures containing PPD and hydrogen peroxide.
- IARC 1978, AICIS 2014
  - In 1978, the International Agency for Research on Cancer (IARC) concluded PPD was not adequately tested in mice by topical application or rats by oral exposure, and, therefore, classified PPD as a Category 3 carcinogen based on a lack of human data and inadequate animal data.
- CIR 2023
  - CIR concluded PPD lacks carcinogenic potential and is safe for use as a hair-dye ingredient in the present uses and concentration.
- Based on the weight of evidence, a score of Moderate was assigned. Available authoritative reviews generally concluded insufficient data, or a lack of carcinogenic concern for PPD alone based on limited experimental data. However, Germany classified PPD to MAK Carcinogen Category 3B based on potential co-carcinogenicity hydrogen peroxide. As this is an authoritative A list for GreenScreen®, ToxServices relied on this listing to score this endpoint.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

PPD was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity reported in well conducted, guideline *in vivo* studies with PPD, supported by expert opinions from SCCP and SCCS. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high based on high quality, measured data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2024a (The authors of the ECHA dossier identified more studies for mutagenicity; however, only the Key *in vivo* and guideline equivalent *in vitro* studies were included due to their higher reliability and adequacy in evaluating this endpoint.)
  - *In vitro*: PPD (purity not reported) was ambiguous in a bacterial reverse mutation assay conducted in a manner similar to OECD Guideline 471 using *Salmonella typhimurium* strains TA102 and TA2638, and *Escherichia coli* strains WP_2 pKM101 and WP_2 *uvr*A pKM101 exposed at up to 5,000 µg/plate with and without metabolic activation. Cytotoxicity was not specified. The authors did not report control data. Positive results were reported in tester strains TA102, WP_2 pKM101 and WP_2 *uvr*A pKM101 without metabolic activation, and negative results were reported for tester strain TA2638 without metabolic activation (Klimisch 2, reliable with restrictions) (034).
  - *In vitro*: PPD (purity not specified, DMSO) was positive in a non-GLP-compliant *in vitro* mammalian chromosome aberration test conducted in a manner similar to OECD Guideline 473 using Chinese hamster ovary (CHO) cells exposed to 15, 29, 58, and 87 µg/mL for 2 hours without metabolic activation. The vehicle, negative, and positive (triethylenemelamine) controls were valid. Cytotoxicity was reported at 29 µg/mL. A dose-related increase in chromosomal aberrations was reported (Klimisch 2, reliable with restrictions) (039). *SCCS (2012) reported a slight increase in the percentage of aberrant cells resulting in positive results for clastogenicity.*

  - *In vivo*: PPD (99.8% purity, deionized water) was not clastogenic in a GLP-compliant mammalian erythrocyte micronucleus test conducted according to OECD Guideline 474. Male and female Wistar rats (6/sex/dose) were administered via gavage a single dose of PPD at 0, 25, 50, or 100 mg/kg and observed 1-, 2-4-, 6-, 24-, and 48-hours post-treatment. Vehicle, negative, and positive (cyclophosphamide (CPA)) controls were valid. There was no increase in the frequency of micronucleated erythrocytes with treatment up to the maximum tolerated dose of 100 mg/kg. The test substance did not exert any cytotoxic effects in the bone marrow. Orange to dark yellow urine color was reported in all treatment animals indicating systemic distribution and bioavailability of PPD (Klimisch 1, reliable without restriction).
  - *In vivo*: PPD (99.8% purity, carboxymethylcellulose vehicle) was not genotoxic in a GLP-compliant unscheduled DNA synthesis (UDS) assay conducted according to OECD Guideline 486. Male Wistar HanIbm: WIST (SPF) rats (4/dose) were administered single gavage doses of 0, 50, or 100 mg/kg PPD. Vehicle and positive (N,N′dimethylhydrazinedihydrochloride (DMH), and 2-aminofluorene (2-AAF)) controls were valid. There was no UDS induction in treated animals when compared to controls. No clinical signs of toxicity were reported. Orange to dark yellow urine color was reported in all treatment animals indicating systemic distribution and bioavailability of PPD (Klimisch 1, reliable without restriction).
- SCCS 2012, CIR 2023, ECHA 2024a
  - *In vivo*: In an *in vivo* Comet assay conducted according to OECD Guideline 489 (GLP unspecified), male Sprague-Dawley Crl:CD (SD) IGS rats (3-5/group) were administered three gavage doses of 0, 25, 50, or 100 mg/kg PPD (purity not specified) in 0.9% physiological saline 24 and 21 hours apart. The animals were sacrificed 3 and 24 hours later and glandular stomach and liver samples were isolated. Vehicle and positive (ethyl methanesulfonate (EMS)) controls were valid. Toxicity was reported at the highest dose tested. No increased DNA damage was observed in the liver and stomach. The study authors concluded PPD was not genotoxic under the conditions of this study (Klimisch 2, reliable with restrictions).
- SCCP 2006, SCCS 2012
  - Positive results were reported in non-GLP-compliant, non-guideline *in vitro* studies with PPD and surrogate PPD HCl. Therefore, they only provided limited evidence of the *in vitro* genotoxicity of PPD.
  - Further studies were conducted and found that, in the absence of oxidizing agents (e.g., hydrogen peroxide), the genotoxicity of PPD seen *in vitro* does not lead to genotoxic effects *in vivo*.
- Based on this weight of evidence, a score of Low was assigned. Positive results were reported in guideline or guideline equivalent *in vitro* studies for gene mutation and chromosomal aberration. However, negative results were reported in high-quality *in vivo* OECD Guideline 474 micronucleus assay for clastogenicity in mice, OECD Guideline 486 UDS study for induction of DNA damage in rats, and OECD Guideline 489 equivalent comet assay for DNA strand breaks in rats. These three *in vivo* studies in combination evaluated both mutagenicity and clastogenicity, indicating PPD had no genotoxic potential *in vivo*. GHS criteria for classification for mutagenicity is predominantly based on *in vivo* data for mutagenicity and clastogenicity indicating results from *in vivo* studies weigh more heavily than *in vitro* data (UN 2023). Based on negative results reported in high-quality *in vivo* mutagenicity and clastogenicity studies, ToxServices did not classify PPD as a mutagen/genotoxicant under GHS criteria, which is equivalent to a GreenScreen® score of Low.

Reproductive Toxicity (R) Score (H, M, or L): *M*

PPD was assigned a score of Moderate for reproductive toxicity based on decreased sperm count, increased abnormal sperm morphology, decreased testicular weights, increased germ cell apoptosis and sloughing of testicular cellular layers in male rats dosed with PPD on the skin for 90 days. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity (CPA 2018b). The confidence in the score is low due to lack of similar findings in other repeated dose and reproductive toxicity studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Bharali and Dutta 2012, U.S. EPA 2016
  - Male Sprague-Dawley rats were exposed to 1,2, or 3 mg/kg PPD via skin painting for 90 days to mimic the actual PPD dosage of 1-3% in hair dyeing formulations. Treatment related effects were reported including decreased sperm count, increased abnormal sperm morphology, and decreased testicular weights in the mid- and high-dose groups. Histopathology findings of the testes for the high dose animals included increased germ cell apoptosis and sloughing of testicular cellular layers.
- ECHA 2024a, CIR 2023
  - *Dermal*: In a non-guideline two-generation reproductive toxicity study (GLP unspecified), male and female Sprague Dawley rats (F0: 40/sex/dose, F1: 20/sex/dose) received topical applications of a hair dye formulation containing 2, 3, or 4% PPD (purity unspecified) in 6% hydrogen peroxide (1:1 v/v) twice weekly during the growth, mating, gestation, and lactation for the F0 generation and from gestation to weaning for the F1 and F2 generations. For the F0 generation, there were no treatment related effects on the fertility indices of the parents, or on gestation, lactation, and weaning indices. For the F1 and F2 generations, there were no treatment related effects on fertility, gestation, or fetal viability indices. The study authors concluded there were no adverse effects on reproduction up to the highest dose tested of 4% in an oxidative hair dye (Klimisch 2, reliable with restrictions).
  - *Dermal*: In a non-GLP-compliant, non-guideline one-generation reproductive toxicity study (GLP unspecified), male and female Sprague Dawley rats (F0: 40/sex/dose, F1: 20/sex/dose) received topical applications of a hair dye formulation containing 2.2% PPD in 6% hydrogen peroxide (1:1 v/v) twice weekly for 10 weeks. Males were treated for 2 weeks prior to mating, through mating and until necropsy, and females were treated through mating, gestation, and lactation for the F0 generation and from gestation to weaning (PND 21) for the F1 generation. There were no treatment related effects on the fertility indices of the parents, or on gestation, lactation, and weaning indices. Fertility rates were higher than controls for both generations; however, the average litter sizes for were identical to controls at 11 live pups per litter. The study authors concluded there were no adverse effects on reproduction up to the dose 2.2% PPD in an oxidative hair dye (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a conservative Moderate score was assigned. A non-guideline 90-day study reported male reproductive toxicities in rats at dermal doses as low as 2 mg/kg/day. The magnitude of change was not reported in the abstract available, and no mating was performed to determine if these effects affected the fertility of the animals. On the other hand, non-guideline one- and two-generation studies with PPD in hair dye formulation mixtures did not identify any reproductive toxicities in rats, at similar doses (up to 4%). Further, no reproductive organ toxicities were observed in repeated dose oral toxicity studies summarized below. Therefore, the

toxicological significance of the findings from the single dermal 90-day study is questionable, and the confidence in the score is reduced.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
PPD was assigned a score of Moderate based on an equivocal increase in early fetal resorption and nonsignificant decrease in fetal body weight at 20 mg/kg/day, a maternally toxic dose, in a prenatal developmental toxicity study in rats on the target chemical. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicities (CPA 2018b). The confidence in the score is low as the significance of the developmental toxicities is uncertain due to limited reporting, and it is uncertain if they are secondary to maternal toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - MAK – Pregnancy Risk Group C
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2024a, CIR 2023, U.S. EPA 2016
  - *Oral*: In a GLP-compliant prenatal developmental toxicity study conducted according to OECD Guideline 414, pregnant Sprague-Dawley Crl: OFA (SD) rats (25/dose) were administered PPD (purity 99.8%) via gavage at doses of 5, 10, and 20 mg/kg/day from gestation day (GD) 6 to 19. For the dams, there were no mortalities and no treatment related effects reported for clinical signs of toxicity, food consumption, ovaries and uterine content, pre- and post-implantation indices, mean litter size, fetal sex ratio or gross pathology. Offspring were evaluated for survival, number and sex of pups, body weight, and external and internal abnormalities. For the mid and high dose dams, a slight reduction in mean gestation body weight gain was reported during the first 3 days; however, this was transient without affecting other parameters, and body weight gain in the low dose group was comparable to controls throughout the study. At the high dose, an equivocal increased incidence of early resorptions was reported. A slight non-significant reduction in mean fetal weight and in mean gravid uterine weight was found for the high dose group compared to controls. There were no malformations or adverse treatment-related variations reported for the offspring. The authors of the REACH dossier identified a maternal toxicity NOEL of 5 mg/kg/day based on slight transient reduction in body weight gain in the mid- and high- dose groups, and a developmental toxicity NOAEL of 10 mg/kg/day based on the increased incidence of early resorptions and nonsignificant decrease in fetal body weight in the high dose group (Klimisch 1, reliable without restrictions). *For this study, U.S. EPA (2016) identified a maternal toxicity NOAEL and LOAEL of 5 and 10 mg/kg/day, respectively, and a developmental toxicity NOAEL and LOAEL of 10 and 20 mg/kg/day, respectively. Furthermore, U.S. EPA notes that the biological significance of the decrease in fetal body weight is uncertain because the magnitude of change was not reported.*
  - *Oral*: In a non-GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, pregnant Sprague-Dawley rats (25/dose) were administered PPD (purity 99.78%) in water via gavage at doses of 5, 10, 15, 20 and 30 mg/kg/day on GD 6 - 15. Dams were evaluated for mortality, clinical signs of toxicity, body weight/weight gain, food consumption, ovarian and uterine indices (i.e., number of corpora lutea, implantation sites per dams, number of resorptions, sex ratio, number of live fetuses per litter), and gross pathology. Offspring were evaluated for body weight, external malformations, and visceral anomalies. At the high dose, 3/25 dams died in the first 4 days of dosing. A reduction in mean gestation body weight gain and on food intake on GD 0 – 12

and 0 – 15 for the 20 and 30 mg/kg dams, respectively, was reported; however, the overall body-weight change from GD 0 – 20 was comparable to controls. No treatment related effects on fetal parameters were reported. The authors of the REACH dossier identified a maternal toxicity NOEL of 10 mg/kg/day based on reduction in body weight during the dosing period, and a developmental toxicity NOEL of 30 mg/kg/day, the highest dose tested (Klimisch 2, reliable with restriction). *For this study, U.S. EPA (2016) identified a maternal toxicity NOAEL and LOAEL of 15 and 20 mg/kg/day, respectively, based on significantly lower body-weight gain and reduced feed intake on GD 0 – 15, and a developmental toxicity NOAEL 30 mg/kg/day, the highest dose tested. Additionally, U.S. EPA noted the highest dose, 30 mg/kg/day, is the Frank Effect Level (FEL) for maternal toxicity, which is the dose that produces significant irreversible, adverse effects.*

- ECHA 2024a, CIR 2023
    - *Dermal*: In the previously described non-guideline two-generation reproductive toxicity study (GLP unspecified), male and female Sprague Dawley rats (F0: 40/sex/dose, F1: 20/sex/dose) received topical applications of a hair dye formulation containing 2, 3, or 4% PPD (purity unspecified) in 6% hydrogen peroxide (1:1 v/v) twice weekly during the growth, mating, gestation, and lactation for the F0 generation and from gestation to weaning for the F1 and F2 generations. For the F1 and F2 generations, there were no treatment related effects on gestation or fetal viability indices. The study authors concluded there were no adverse effects on development up to the highest dose tested of 4% in an oxidative hair dye (Klimisch 2, reliable with restrictions).
    - *Dermal*: In the previously described non-GLP-compliant, non-guideline one-generation reproductive toxicity study (GLP unspecified), male and female Sprague Dawley rats (F0: 40/sex/dose, F1: 20/sex/dose) received topical applications of a hair dye formulation containing 2.2% PPD in 6% hydrogen peroxide (1:1 v/v) twice weekly for 10 weeks. Males were treated for 2 weeks prior to mating, through mating and until necropsy, and females were treated through mating, gestation, and lactation for the F0 generation and from gestation to weaning (PND 21) for the F1 generation. There were no treatment related effects on gestation, lactation, and weaning indices. The study authors concluded there were no adverse effects on development up to the dose 2.2% PPD in an oxidative hair dye (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Moderate was assigned. Among the studies identified, the only study that reported developmental effects is a GLP-compliant, OECD Guideline 414 study in rats, which reported an equivocal increase in early fetal resorption and nonsignificant decrease in fetal body weight at 20 mg/kg/day, a maternally toxic dose, in a prenatal developmental toxicity study in rats on the target chemical. The U.S. EPA noted the biological significance of the reduction in fetal body weight was uncertain due to insufficient data in regard to the magnitude of the change. MAK listed PPD as a Pregnancy Risk Group C for developmental toxicity which corresponds to a score of Low or Moderate; but the basis of the listing could not be identified. Therefore, ToxServices conservatively assigned a Moderate score assuming the observed developmental effects were independent of maternal toxicity.

Endocrine Activity (E) Score (H, M, or L): *M*

PPD was assigned a score of Moderate for endocrine activity based on TEDX listing and mixed high throughput screening assay results. GreenScreen® criteria classify chemicals as a Moderate to High hazard for endocrine activity when they are listed on TEDX for endocrine effects. The preliminary score of Moderate is raised to High when there are evidence of endocrine-mediated effects leading to High scores for carcinogenicity, reproductive toxicity, developmental toxicity, repeated dose systemic

toxicity, and repeated dose neurotoxicity (CPA 2018). Although PPD appeared to induce male reproductive effects, and systemic toxicity, there was no evidence that such effects were endocrine-mediated. Therefore, the preliminary score of Moderate was maintained. The confidence in the score is low as there were no evaluations of circulating hormones nor endocrine organs reported in studies identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - TEDX – Potential Endocrine Disruptor
- U.S. EPA 2024b
  - PPD was active in 4/18 estrogen receptor (ER) assays, 3/14 androgen receptor (AR) assays, 2/7 steroidogenesis assays, and 1/10 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (Appendix E).
- TEDX 2018
  - The TEDX entry for PPD includes the following reference:
  - Bharali and Dutta 2012, U.S. EPA 2016
    - Male Sprague-Dawley rats were exposed to 1,2, or 3 mg/kg PPD via skin painting for 90 days. Treatment related effects were reported including decreased sperm count, increased abnormal sperm morphology, and decreased testicular weights in the mid- and high-dose groups. Histopathology findings of the testes for the high dose animals included increased germ cell apoptosis and sloughing of testicular cellular layers. Study authors measured increased lipid peroxidation in the testicular tissue and indicated that the reproductive organ toxicities may be attributed to oxidative stress.
- ECHA 2024a, U.S. EPA 2016
  - *Oral*: In a GLP-compliant repeated dose oral toxicity study conducted in a manner similar to OECD Guideline 408, male and female Crl:CD(SD)BR rats (15/sex/dose) received gavage doses of 2, 4, 8, and 16 mg/kg PPD (actual dose ingested, purity not specified) in water for 90 days. Significant variations in absolute and relative thyroid weights were reported in high dose males; however, the study authors did not consider this an adverse effect due to a lack of associated pathological changes and/or lacked a dose-response (Klimisch 1, reliable without restriction) (001). *U.S. EPA (2016) noted that although the study authors indicated the thyroid weights of the controls were unusually low, there was no dose-response relationship identified, and therefore changes in thyroid weight for high dose males were not considered treatment related.*
- There were no evaluations of circulating hormones reported in repeated dose toxicity studies identified for the target chemical.

<u>Group II and II* Human Health Effects (Group II and II* Human)</u>

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): H

PPD was assigned a score of High for acute toxicity based on the most conservative oral LD_{50} value of 75 mg/kg in rats, aerosol inhalation LC_{50} of 0.92 mg/L (calculated) and association with the EU harmonized H301, H311, and H331. GreenScreen® criteria classify chemicals as a High hazard for acute toxicity when oral LD_{50} values are > 50 - 300 mg/L and aerosol LC_{50} values are > 0.5 – 1.0 mg/L

and when associated with EU-GHS authoritative listings of H301 or H311 or H331 (CPA 2018b). The confidence in the score was high as it was based on reliable measured data on the target chemical and authoritative listings.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU – GHS (H-statements) Annex 6 Table 3-1 – H301 – Toxic if swallowed [Acute toxicity (oral) – Category 3]
        - EU – GHS (H-statements) Annex 6 Table 3-1 – H311 – Toxic in contact with skin [Acute toxicity (dermal) – Category 3]
        - EU – GHS (H-statements) Annex 6 Table 3-1 – H331 – Toxic if inhaled [Acute toxicity (inhalation) – Category 3]
        - DOT Class 6.1 Group III
    - *Screening:*
        - GHS – New Zealand – Acute oral toxicity – Category 3
            - Based on its association with the R Phrase R25: Toxic if swallowed, from company data (CCID 2024).
        - GHS – New Zealand – Acute dermal toxicity – Category 3
            - Based on its association with the R Phrase R24: Toxic in contact with skin, from company data (CCID 2024).
        - GHS – New Zealand – Acute inhalation toxicity – Category 3
            - Based on its association with the R Phrase R23: Toxic if inhaled, from company data (CCID 2024).
        - GHS – Japan – H301 – Toxic if swallowed [Acute toxicity (oral) – Category 3]
            - Based on oral LD_{50} values of 80 - 98 mg/kg in rats (NITE 2006, 2011).
        - GHS – Japan – H331 – Toxic if inhaled [Acute toxicity (inhalation) – Category 3]
            - Based on inhalation LC_{50} values of 0.92 mg/L/4 hours in rats, and because this value is above the saturated vapor pressure concentration of 0.0291 mg/L, the reference value for dusts was used (NITE 2006, 2011).
        - GHS – Australia – H301 – Toxic if swallowed [Acute toxicity (oral) – Category 3]
        - GHS – Australia – H311 – Toxic in contact with skin [Acute toxicity (dermal) – Category 3]
        - GHS – Australia – H331 – Toxic if inhalation [Acute toxicity (inhalation) – Category 3]
        - GHS – Korea – H301 – Toxic if swallowed [Acute toxicity (oral) – Category 3]
        - GHS – Korea – H311 – Toxic in contact with skin [Acute toxicity (dermal) – Category 3]
        - GHS – Korea – H331 – Toxic if inhalation [Acute toxicity (inhalation) – Category 3]
        - GHS – Malaysia – H300 – Fatal if swallowed [Acute toxicity (oral) – Category 1 or 2]
        - GHS – Malaysia – H311 – Toxic in contact with skin [Acute toxicity (dermal) – Category 3]
        - GHS – Malaysia – H331 – Toxic if inhalation [Acute toxicity (inhalation) – Category 3]
- ECHA 2024a (The authors of the ECHA dossier identified more studies for acute toxicity; however, only the Key, GLP and guideline studies, and/or Klimisch 1 or Klimisch 2 studies were included due to their higher reliability and adequacy in evaluating this endpoint).

  - *Oral*: LD_{50} (GLP-compliant, OECD Guideline 420) = 75 mg/kg in female Sprague-Dawley Crl:OFA(SD) rats (Klimisch 1, reliable without restriction). 1/1 animal died at 100 mg/kg, ½ at 75 mg/kg, 0/1 at 50 mg/kg, and 0/1 at 25 mg/kg/.
  - *Dermal*: LD_{50} (non-GLP-compliant) > 7,940 mg/kg in male and female New Zealand White rabbits exposed to a 40% aqueous solution of PPD in an unspecified vehicle (Klimisch 2, reliable with restrictions).
  - *Inhalation*: nose-only, 4h LC_{50} (GLP not specified, equivalent to OECD Guideline 403) = 0.92 mg/L air (calculated) in male Crl:CD rats exposed to < 0.54 mg/L vapor and ≥ 0.54 mg/L aerosol of PPD (99.5% purity) (Klimisch 2, reliable with restrictions).
- SCCP 2006
  - *Oral*: LD_{50} = 80-100 mg/kg in rats, 290 mg/kg in mice, 250 mg/kg in rabbits, and 100 mg/kg in cats.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score (vH, H, M, or L): *vH*

PPD was assigned a score of Very High for systemic toxicity (single dose) based on evidence of systemic toxicity to the muscles, heart, and/or kidneys in humans and mice at oral doses of ≥ 80 mg/kg. PPD is also associated with a GHS – Japan listing as a Category 1 specific target organ/systemic toxicant – following single exposure. GreenScreen® criteria classify chemicals as a Very High hazard for systemic toxicity (single dose) when single exposure systemic toxicity oral LOAELs are ≤ 300 mg/kg (CPA 2018b). The confidence in the score is low as it is based on limited human case reports and animal data with support from a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS Japan – H370 – Causes damage to organs [Specific target organs/systemic toxicity following single exposure – Category 1].
- NITE 2011
  - GHS Japan classified PPD as a GHS Category 1 specific target organ toxicant – single exposure (heart, muscle, kidney) based on "multiple case reports of dyspnea and edema of the face, neck, tongue or throat after oral exposure in addition to increased blood CPK, oliguria, renal tubular degeneration, and rhabdomyolysis [which is the release of proteins and electrolytes into the blood when muscle tissue is damaged], leading to acute renal failure and death in some cases."
- ECHA 2024a
  - *Oral:* As previously described, a GLP-compliant oral acute toxicity study conducted according to OECD Guideline 420 with female Sprague-Dawley Crl:OFA(SD) rats, reported a minimum lethal dose of 75 mg/kg. In an up and down procedure, animals (n=1, 1, 2 and 1 at 25, 50, 75, and 100 mg/kg, respectively) were administered a single gavage dose of 25, 50, 75, or 100 mg/kg PPD (99.8% purity) in sterile water. The first animal received 100 mg/kg, exhibited clinical signs of toxicity prior to death within 90 minutes. One female was administered 75 mg/kg, and as no death occurred within 90 minutes, another female received 75 mg/kg to confirm toxicity; however, this female died within 2 hours and 45 minutes after treatment. The one female treated with 50 mg/kg survived, but exhibited severe clinical signs of toxicity. Clinical signs of toxicity observed at greater than and equal to 50 mg/kg included marked subdued behavior, unsteady gait, loss of balance, lateral decubitus, piloerection, and/or tremors. No mortality or clinical signs of toxicity were reported for the 1 female administered 25 mg/kg; however, orange stained bedding was observed and

considered due to the orange-colored urine likely from the dye. Gross pathological findings were normal for all animals at necropsy. No information was provided on body weights. The study authors identified a NOAEL of 25 mg/kg (Klimisch 2, reliable with restrictions). *Although no information was provided for specific body weights, ToxServices inferred that body weights were not affected by the treatment. Furthermore, clinical signs of incoordination, piloerection, and/or tremors were evaluated under neurotoxicity – single exposure.*

  - *Oral*: The authors of the ECHA dossier for PPD also noted in the endpoint summary for acute toxicity that "rhabdomyolysis was observed in mice and humans at an oral dose level around or below 80 mg/kg."
  - *Dermal*: As previously described, a non-GLP-compliant dermal acute toxicity study with male and female New Zealand White rabbits (n=3) exposed to topical applications of a 40% aqueous solution of PPD (purity and vehicle not specified) for 24 hours under an unspecified coverage condition and observed for 14 days, reported an LD_{50} of > 7,940 mg/kg. No mortalities and no treatment related effects on gross pathology were observed. Weight loss was observed 2-4 days after dosing. No information was provided on clinical signs of toxicity (Klimisch 2, reliable with restrictions). *Additional dermal studies were provided in the REACH dossier for PPD; however, these studies were non-guideline, at lower doses of PPD, and with limited reporting; therefore, these studies were not summarized here.*
  - *Inhalation*: As previously described, an inhalation acute toxicity study conducted in a manner similar to OECD Guideline 403 (GLP unspecified) with male Crl:CD rats, reported a 4-hour nose-only aerosol LC_{50} of 0.92 mg/L. Animals (10/concentration) were exposed nose-only to concentrations of 0.07, 0.30, 0.54, 0.94, or 1.8 mg/L PPD (99.5% purity) and the study authors reported at concentrations < 0.54 mg/L and ≥ 0.54 mg/L PPD was in vapor and aerosol form, respectively. All deaths occurred within 48 hours with 0/10, 1/10, 4/10, 5/10, and 7/10 deaths reported at 0.07, 0.30, 0.54, 0.94, or 1.8 mg/L, respectively. No overt clinical signs of toxicity were observed at the lowest concentration. Cyanosis was observed at the highest concentration, with red nasal discharge reported at higher concentrations, and red ocular discharge or brown stained fur found at all concentrations. Dose-dependent, light to severe weight loss was reported for 3 days after which weight gain was measured in all groups. The authors of the ECHA dossier noted in the acute toxicity summary that central nervous system effects were observed in this study, including a lack of righting reflex and tremors (Klimisch 2, reliable with restrictions). *Clinical signs of cyanosis and red nasal discharge are signs of respiratory irritation. Lack of righting reflex and tremors are signs of neurotoxicity, and, therefore, were considered separately under single dose neurotoxicity in this report.*
- SCCP 2006
  - PPD's very low dermal absorption potential, < 1% as assessed *in vitro* in excised human skin and *in vivo* in humans and non-human primates (using urinary excretion of PPD metabolites as a biomarker), suggests that systemic effects at distal sites are unlikely to result from brief topical exposures to this ingredient.
- Based on the weight of evidence, a score of Very High was assigned. Clinical signs of respiratory irritation and neurotoxicity were reported in the acute inhalation toxicity study conducted in a manner similar to OECD Guideline 403. Additionally, in an OECD Guideline 420 study in rats, a NOAEL of 25 mg/kg was identified by the study authors; however, the "severe" clinical signs of toxicity reported including incoordination, piloerection, and/or tremors may be due to neurotoxicity that is evaluated separately in this report. Nevertheless, rhabdomyolysis has been reported in both mice and humans with oral exposures ≥ 80 mg/kg PPD. GHS criteria indicates a chemical may be

classified as a Category 1 specific target organ toxicant following single exposure when "observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations" (UN 2023). Therefore, based on evidence of severe systemic effects to the muscle, heart, and kidneys in mice and humans at ≥ 80 mg/kg, which is ≤ 300 mg/kg, the cut-off value for classification as a GHS Category 1 specific target organ toxicant – single exposure, a conservative score of Very High was assigned.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score (H, M, or L): H

PPD was assigned a score of High for systemic toxicity (repeated dose) based on the lowest LOAEL of 8 mg/kg/day for increased liver and kidney weights in females in a subchronic oral exposure study in rats exposed to PPD, resulting in ToxServices classifying PPD as a GHS Category 1 systemic toxicant (repeated exposure). GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when subchronic oral LOAELs are ≤ 10 mg/kg/day, and they are classified as GHS Category 1 for systemic toxicity - repeated exposure (CPA 2018b). Confidence is high as it is based on a reliable experimental study on the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - GHS Japan – H372 – Causes damage to organs through prolonged or repeated exposure [Specific target organs/systemic toxicity following repeated exposure – Category 1].
- NITE 2011
    - GHS Japan classified PPD as a GHS Category 1 specific target organ toxicant – repeated exposure (liver, nervous system, and kidney) and Category 2 (heart, muscle) based on case reports of humans exposed to commercially available hair dyes or in occupational settings in which effects on the liver, kidney, cardiovascular, immune, and nervous systems were reported. Additionally, at 10 mg/kg, which is within the guidance value cutoff for GHS Category 1, rabbits exhibited alterations of the myocardial parenchyma (i.e., edema, swelling of muscle) in an oral 90-day study.
- ECHA 2024a (The authors of the ECHA dossier identified additional studies for systemic toxicity – repeated dose; however, only Key and guideline or guideline equivalent studies were included due to their higher reliability and adequacy in evaluating this endpoint.)
    - *Oral*: In the previously described GLP-compliant repeated dose oral toxicity study conducted in a manner similar to OECD Guideline 408, male and female Crl:CD(SD)BR rats (15/sex/dose) received gavage doses of 2, 4, 8, and 16 mg/kg PPD (actual dose ingested, purity not specified) in water for 90 days. Animals were evaluated for clinical signs of toxicity, body weight/weight gain, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histology. Clinical signs of convulsions in one females and hunched posture, hypoactivity, pale extremities, and irregular respiration were reported for another female; however, the study authors did not consider these clinical signs to be treatment related as they were not observed in other animals. A slight reduction (8%) in body weight gain was reported in males in the 8 mg/kg group, and body weight gain was similar to controls in all remaining treatment animals; therefore, the study authors did not consider the reduction in the high dose males to be treatment related. Slight variations in hematology and clinical chemistry were within historical controls or small and lacked dose-response, and significant variations

in absolute and relative liver (males/females) and kidney (females) weights had no associated pathological changes and/or lacked a dose-response, and therefore, were not considered to be treatment related by the study authors. The study authors identified a systemic toxicity NOAEL of 16 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction) (001). *U.S. EPA (2016) considered the variations in absolute and relative organ weights to be statistically significant and biologically significant based on the magnitude of the difference to controls. At the highest dose tested, 16 mg/kg, the absolute liver weights for males and females were increased by 12% compared to controls, and the relative liver weights for males and females were increased by 12% and 10%, respectively. For the high dose females, the absolute and relative kidney weights were increased by 16% and 14% compared to controls. Overall, U.S. EPA identified a NOAEL and LOAEL of 4 and 8 mg/kg/day, respectively, based on the > 10% increase in relative kidney and liver weight in female rats. U.S. EPA (2016) used a NOAEL of 4 mg/kg for increased relative kidney weight and $BMDL_{10}$ of 4 mg/kg for increased relative liver weight as its point of departures (POD) to derive the provisional subchronic reference dose (p-RfD) of 1 x 10^{-2} mg/kg/day and to derive the chronic p-RfD of 1 x 10^{-3} mg/kg/day.*

- CIR 2023, U.S. EPA 2016, ECHA 2024a
    - *Oral:* In a chronic dietary study, male and females F344 rats (63-66/sex/treatment, 24-25/sex/control) were provided feed containing 0.05 or 0.1% PPD (purity not specified) (equivalent to 0, 38.8, and 77.6 mg/kg in males and 0, 46.1, and 92.1 mg/kg in females as identified by U.S. EPA) for 80 weeks. Animals were evaluated for clinical signs of toxicity, body weights, food intake, hematology, histology, and gross pathology of all organs. Only one female and 6 males survived to week 80, and only one male survived from the control group. Throughout the study, body weights for all treatment groups of males and the low-dose females were comparable to controls; however, the high-dose females did exhibit a ≤ 10% and 21% decrease in body weights throughout and at the end of the study, respectively, and high-dose males exhibited a 14% decreased at the end of the study (Klimisch 2, reliable with restrictions) (003). *U.S. EPA (2016) did not consider this and other identified chronic toxicity studies sufficient for evaluating PPD due to poor quality and reporting.*
- SCCNFP 1999, SCCP 2006, AICIS 2014, ECHA 2024a
    - *Dermal:* In a long-term topical study, female mice and female rabbits (50/group) received topical applications of 5% or 10% PPD (purity unspecified) in 0.02 mL acetone to the shaved, intact skin, twice a week until spontaneous death occurred (up to 135 weeks for mice and 85 weeks for rabbits). There were no mortalities, and no treatment related effects on clinical signs of toxicity, body weights, food consumptions, hematology, and urinalysis. No treatment related tumors and no local irritation such as epidermal hyperplasia, ulceration, or dermatitis were reported. Histological examination of lesions of the lung, liver, and kidney were unremarkable (Klimisch 2, reliable with restrictions) (003/004).
    - *Dermal:* In another long-term dermal study, Swiss Webster mice received topical applications of 1%, 2%, 3%, or 4% PPD in four hair dye formulations mixed with 6% hydrogen peroxide (1:1) for 21 to 23 months. No gross or histological abnormalities were reported. No further details were provided.
- SCCS 2016
    - Myocardial damage has been reported in humans with PPD-related hair dye poisonings.
- Based on the weight of evidence, a score of High was assigned. While evidence of systemic toxicity has been found in humans, the effects were reported (i.e., myocardial, kidney, liver damage) in relation to PPD-related hair dye poisoning or occupational exposure case reports. As the human data evaluated PPD in combination with other chemicals and is poorly reported; ToxServices

weighed reliable animal data more heavily than the human data in the weight of evidence. Many subchronic and chronic repeated dose oral and dermal toxicity studies on PPD were non-guideline, performed decades ago, performed on mixtures, and/or were non-GLP compliant. They were judged not appropriate to identify effect levels for risk assessments by U.S. EPA (2016), assigned Klimisch scores of 3 (not reliable) or 4 (not assignable) by REACH dossier authors, or missing critical information to determine the NOAEL/LOAEL. However, U.S. EPA (2016) considered the subchronic oral study in rats conducted in a manner similar to OECD Guideline 408 sufficient for evaluation of PPD and used a POD of 4 mg/kg based on a greater than 10% increase in relative kidney and liver weight in female rats, in deriving the subchronic and chronic p-RfDs for PPD. The LOAEL from this study is 8 mg/kg/day, which is below the GHS cutoff of 10 mg/kg/day for subchronic oral studies (UN 2023). Therefore, ToxServices classified PPD as a Category 1 specific target organ toxicant following repeated inhalation exposure under GHS criteria (UN 2023).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *vH*
PPD was assigned a score of Very High for neurotoxicity (single dose) based on evidence of irreversible narcotic effects at the oral LOAEL of 40 mg/kg/day in a single exposure neurotoxicity study which performed a functional observation battery (FOB), its listing by G&L as a neurotoxicant, and ToxServices classifying PPD as a GHS Category 1 neurotoxicant. GreenScreen® criteria classify chemicals as a Very High hazard for neurotoxicity (single dose) when they are classified as a GHS Category 1 single exposure neurotoxicant and listed by G&L as a neurotoxicant (CPA 2018b). The confidence in the score is low as limited details were reported in the critical study, and the effects occurred in the presence of other systemic toxicity, leading to uncertainty on the specificity of the observed effects.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - G&L – Neurotoxic Chemicals – Neurotoxic
- ECHA 2024a
  - *Oral:* As previously described, in a GLP-compliant mammalian erythrocyte micronucleus test conducted according to OECD Guideline 474, male and female Wistar rats (6/sex/dose) were administered single gavage doses of PPD up to the maximum tolerated dose, 100 mg/kg. Orange to dark yellow urine color was reported in all treatment animals indicating systemic distribution and bioavailability of PPD. Reduction of spontaneous activity was reported at all time points (1 hour to 48 hours post exposure) in surviving top dose animals, and at lower doses (25 and 50 mg/kg) which was reversible at 48 hours post-treatment (Klimisch 1, reliable without restriction).
  - *Oral:* As previously described, a GLP-compliant oral acute toxicity study conducted according to OECD Guideline 420 with female Sprague-Dawley Crl:OFA(SD) rats reported a minimum lethal dose of 75 mg/kg. Clinical signs of toxicity observed at greater than and equal to 50 mg/kg included marked subdued behavior, unsteady gait, loss of balance, lateral decubitus, piloerection, and/or tremors. No mortality or clinical signs of toxicity were reported for the 1 female administered 25 mg/kg. Gross pathological findings were normal for all animals at necropsy. The study authors identified a NOAEL of 25 mg/kg (Klimisch 2, reliable with restrictions).
  - *Inhalation*: As previously described, an inhalation acute toxicity study conducted in a manner similar to OECD Guideline 403 (GLP unspecified) with male Crl:CD rats, reported a 4-hour nose-only aerosol LC_{50} of 0.92 mg/L. Animals (10/concentration) were exposed nose-only to concentrations of 0.07, 0.30, 0.54, 0.94, or 1.8 mg/L PPD (99.5% purity) and

the study authors reported at concentrations < 0.54 mg/L and ≥ 0.54 mg/L PPD was in vapor and aerosol form, respectively. All deaths occurred within 48 hours with 0/10, 1/10, 4/10, 5/10, and 7/10 deaths reported at 0.07, 0.30, 0.54, 0.94, or 1.8 mg/L, respectively. The authors of the ECHA dossier noted that central nervous system effects were observed in this study, including a lack of righting reflex and tremors (dose not specified) (Klimisch 2, reliable with restrictions).

- HSDB 2019
    - In an acute oral neurotoxicity study, Crl:CDBR rats (12/sex/group) received single gavage doses of 0, 20, 40 or 80 mg/kg PPD (purity unspecified). Animals were evaluated for neurotoxic effects via FOB and motor activity tests performed prior to exposure, and at 1.5 hours (time of maximal clinical signs), 24 hours, and 4 days post-treatment. Females of all dose groups and mid- and high-dose males exhibited significantly reduced weight gain in addition to significantly reduced food consumption in mid- and high-dose females after Day 1 and high-dose males. In the FOB, females exhibited significant dose-related malaise, postural changes, palpebral closure (the act of blinking primarily using the upper lid alone), and diminished arousal, and although males also exhibited similar findings, these were not statistically significant compared to controls. There were no treatment related effects on fore- and hind-limb grip strength or foot splay in any group. Decreased motor activity was significant and dose-related, except after Day 1 in both low-dose groups.
- Based on the weight of evidence, a score of Moderate was assigned. Rats exposed nose-only to PPD aerosol exhibited neurotoxic effects including a lack of righting reflex and tremors in an OECD Guideline 403 equivalent study; no pathology findings were reported. In the OECD Guideline 420 study in rats, a NOAEL of 25 mg/kg was identified and the severe clinical signs of toxicity reported at the LOAEL of 50 mg/kg (non-lethal) included marked subdued behavior, unsteady gait, loss of balance, lateral decubitus, piloerection, and/or tremors. However, the reversibility of these effects was not provided, and only one animal was used at 50 mg/kg/day. The animal appeared to have experienced severe systemic toxicity, and the clinical signs were not consistent with narcosis. In a third study, rats exposed to oral doses of up to 80 mg/kg exhibited neurotoxicity in FOBs; however, for the most part, the most significant effects appeared in females only, and a dose-dependent decrease in motor activity was reversible only at the low dose of 20 mg/kg. The effects did not appear to be reversible at 40 mg/kg and hence may require higher GHS classification than Category 3 (transient narcotic effects). Standard acute toxicity studies do not normally include FOBs; therefore, the results of this study carry more weight in the weight of evidence and ToxServices assigned a LOAEL of 40 mg/kg for this study. Overall, the LOAEL of 40 mg/kg/day is below the GHS Category 1 cutoff value of 50 mg/kg/day, and it is below the cut-off value for oral single exposure neurotoxicity of 300 mg/kg/day for a score of Very High based on GreenScreen® criteria. Therefore, ToxServices conservatively classified PPD as an GHS Category 1 neurotoxicant and assigned a score of Very High with low confidence.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG

PPD was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of repeated dose toxicity studies that specifically performed a neurotoxicity assessment, typically including a functional observation test.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - G&L – Neurotoxic Chemicals - Neurotoxic

- No repeated dose toxicity studies that specifically performed a neurotoxicity assessment were identified.
- NITE 2011
    - GHS Japan classified PPD as a GHS Category 1 specific target organ toxicant – repeated exposure (liver, nervous system, and kidney) based on case reports of humans exposed to commercially available hair dyes or in occupational settings in which effects on the nervous systems were reported.
- Although PPD is listed by G&L as a neurotoxicant, this listing considers both acute and repeated neurotoxicity. While limited evidence of neurotoxicity was reported in humans from over or occupational exposures of PDD, often in mixtures, ToxServices did not consider this sufficient for classification as a neurotoxicant with repeated exposure. No clinical signs of neurotoxicity were reported in repeated dose toxicity studies; however, these studies are also insufficient for classification as they lacked a specifically performed neurotoxicity assessment, such as an FOB. Therefore, a Data Gap was assigned for this endpoint.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): H

PPD was assigned a score of High for skin sensitization based on ToxServices classifying PPD as a Category 1A skin sensitizer based on the lowest EC3 value of 0.06%, which is ≤ 2%, from an OECD Guideline 429 local lymph node assay (LLNA) in mice with supporting EC3 values in the range of 0.06 – 0.2% from additional LLNAs in mice and sensitizing potential in humans. Additionally, PPD has an EU harmonized classification as a Category 1 and supporting conclusion by CIR as a skin sensitizer in humans. GreenScreen® criteria classify chemicals as a High hazard for skin sensitization when they are classified to GHS Category 1A classification (CPA 2018b). The confidence in the score is high as it is based on a high quality, reliable study with supporting conclusion by CIR and authoritative and screening listings.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU – GHS (H-statements) Annex 6 Table 3-1 – H317 – May cause an allergic skin reaction [Skin sensitization – Category 1].
        - MAK – Sensitizing Substance (Sh) – Danger of skin sensitization.
    - *Screening:*
        - GHS – Japan – H317 – May cause an allergic skin reaction [Skin sensitization – Category 1A].
            - Based on classification as an occupational skin sensitizer Group 1, and sensitization reactions reported in both animals and humans.
        - GHS – New Zealand – Skin sensitization Category 1.
        - GHS – Australia – H317 – May cause an allergic skin reaction [Skin sensitization – Category 1].
        - GHS – Korea – H317 – May cause an allergic skin reaction [Skin sensitization – Category 1].
        - GHS – Malaysia – H317 – May cause an allergic skin reaction [Skin sensitization – Category 1].
- ECHA 2024a
    - In a GLP-compliant LLNA conducted according OECD Guideline 429 and Directive 96/54/EEC, Part B.6 (30 July 1996), female CBA/J mice (5/dose) were administered 0, 0.05, 0.25, or 1.25% of PPD (100% purity) in acetone/olive oil (4:1 v/v) to the dorsal skin of the ears for five consecutive days. The mean stimulation indices (SI) based on the increase in 3H-methylthymidine (3H-TdR) compared to controls were reported to be 2.6, 10.4, and 16.1

for the 0.05, 0.25, and 1.25% dose groups, respectively. The calculated EC3 value was 0.06%. The study authors concluded PPD was a delayed contact sensitizer based on an EC3 ≤ 2% (Klimisch 1, reliable without restriction).
    - The authors of the ECHA dossier evaluated 10 studies from 1998 to 2005, and identified EC3 values for PPD in the range of 0.06 – 0.18. The authors of the ECHA dossier considered the average EC3 value of 0.11% as the most appropriate value reflecting the skin sensitization potential of PPD.
- SCCP 2006, SCCS 2012
    - PPD caused dermal sensitization in 100% of laboratory animals (guinea pigs and mice). The skin sensitization potency was estimated in multiple mouse local lymph node assays (LLNAs) in two laboratories; the EC3 value for PPD was 0.06-0.2%.
- SCCP 2006, SCCS 2012
    - There is strong evidence that PPD is also a strong contact allergen in humans; it is one of the most common causes of skin sensitization. Standard patch tests in more than 36,000 eczema patients in Germany identified a standardized contact allergy rate of 4.8%. Patch testing conducted in PPD-allergic patients showed that 6/16 of them reacted to 1% PPD after only 15 minutes of exposure. There have been some rare case reports of anaphylaxis arising from dermal contact with PPD in hair dyes.
    - Despite the increased use of hair dyes, the incidence of positive patch tests to PPD in eczema patients has remained stable over the past 30 years. This may be due to: higher dye purity; improved formulation technology; clear use instructions; and warnings on package labels. Hair dye allergic contact dermatitis, however, is common and can often lead to very severe bouts of oozing scalp dermatitis requiring treatment by a doctor and treatment with systemic corticosteroids.
- SCCS 2012
    - "The frequency of immediate hypersensitivity reactions to PPD are unknown, and severe reactions appear to be rare in comparison" to the low concentration of PPD in hair dye formulations.
- CIR 2023
    - In a human repeat insult patch test (HRIPT), 98 healthy subjects received induction applications of a 2 cm^2 patch containing 1% PPD (purity not specified) in petroleum under occlusive conditions for 5 minutes, 3 times a week. For challenge, patches were left in place for 48 hours and observations were made 30 minutes and 48 hours post-application. The study authors determined 1 subject (1/98 = 1.02%) to be pre-sensitized, 3/98 (3.06%) subjects to be sensitized, and 2/98 (2.04%) subjects had irritant reactions.
    - In a 6-month in use clinical study, a low incidence of sensitization in a pre-screening test was reported in 69/2545 subjects (2.7%) exposed to 1% PPD under occlusive conditions, and these subjects were excluded from the main study. The remaining 2,476 subjects were split among three test groups for the main study. Group 1 was induced with a hair dye formulation containing 0.96% PPD 5 minutes/day for the first 4 days, then 5 minutes/once per week. Group 2 was induced with a hair dye formulation containing 3% PPD 30-40 minutes/once a month for a total of 6 exposures, and Group 3 was unexposed. All three groups were allowed a 3- to 4-week rest period and then challenged with 1% PPD in petroleum for 48 hours under open conditions. At the end of challenge, 7.2%, 1.3%, and 0.4% of subjects from Groups 1, 2, and 3, respectively, had positive reactions, and the majority of reactions were Grade 1. The study authors concluded the duration affected the rate of sensitization, based on 54% and 3% sensitization reactions observed after 48 hour and 5 minute exposures, respectively. Furthermore, the study authors concluded that

infrequent, longer duration, higher concentration exposures to PPD were less likely to induce sensitization than frequent, short durations, lower concentration exposures.

- Based on the above data, a score of High was assigned. Numerous LLNAs in mice reported EC3 values less than or equal to 0.2%. For the weight of evidence evaluation, ToxServices weighed the animal data more heavily than the human data. GHS criteria indicate that "human data [are] not generated in controlled experiments [(i.e., human repeat insult patch tests (HRIPT)] with volunteers for the purpose of hazard classification can be used with caution" (UN 2023). Although human studies report positive responses, some clinical studies were performed in sensitive populations such as eczema patients and/or PPD-allergic patients, leading to uncertainty regarding the cause of the positive reactions reported. In an HRIPT reported by CIR (2023), a sensitization rate of 3.06% was reported with induction applications of 1% PPD. However, in a 6-month in-use clinical study, mostly Grade 1 positive reactions were reported in 7.2, 1.3, and 0.4% subjects induced with 1% PPD for short, frequent exposure, 3% PPD for infrequent, longer duration, and without exposure to PPD, respectively, and challenged with 1% PPD for 48 hours. CIR (2023) concluded that PPD is "a known skin sensitizer and some persons may be sensitized under intended conditions of use." Lastly, PPD has a harmonized EU listing as a Category 1 skin sensitizer and a MAK listing as a sensitizing substance. Based on the EC3 values of 0.06-0.2%, which are less than 2%, reported in numerous LLNAs, in addition to sensitization reactions reported in humans and CIR's conclusion PPD is a skin sensitizer in humans, ToxServices classified PPD as a Category 1A skin sensitizer.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *M*

PPD was assigned a score of Moderate for respiratory sensitization based on positive skin sensitization potential and the presence of a structural alert for respiratory sensitization, and the occurrence of asthmatic reactions in workers, classifying it to GHS Category 1 for respiratory sensitization, according to ECHA guidance (2017). This is consistent with the screening GHS Japan Category 1 listing. GreenScreen® criteria classify chemicals as a Moderate hazard for respiratory sensitization when available data indicate that GHS Category 1B classification for respiratory sensitization (Low frequency) is warranted (CPA 2018b). The confidence in the score is low due to lack of sufficient information to differentiate between Moderate (Category 1B) and High (Category 1A).

- Authoritative and Screening Lists
  - *Authoritative:*
    - AOEC – Asthmagens – Suspected asthmagen (R) – but does not meet AOEC criteria.
  - *Screening:*
    - GHS – Japan – H334 – May cause allergy or asthma symptoms or breathing difficulties if inhaled [Respiratory sensitizer – Category 1].
      - Based on reports of workers who developed allergic asthma from occupational exposure and inflammation of the pharynx by direct irritation, in addition to very small quantities of PPD reported to cause asthma after 3 months to 10 years of exposure (NITE 2011).
  - *Other:*
    - CHE – Toxicant Database – Asthma – allergen, sensitizer – strong evidence.
    - Quebec CSST – Asthma Agents – Agent causing occupational asthma.
- MAK 2000
  - PPD was first associated with respiratory sensitization as early as the end of the 19th century with increased incidence of asthma reported in the workers in the fur dyeing and later the hair dyeing industries; however, these symptoms were not associated with allergic effects until the 1920s.

  - Respiratory allergy to PPD has not been conclusively verified; therefore, it is not designed as "Sa".
- OECD 2023
  - PPD contains a structural alert for respiratory sensitization – Pro-Michael addition (Appendix D).
- Based on the weight of evidence, a score of Moderate was assigned. PPD does contain a structural alert: Pro-Michael addition for respiratory sensitization (OECD 2023). PPD is a skin sensitizer based on positive animal and human data (see skin sensitization section above) in addition to an EU harmonized listed as a Category 1 skin sensitizer. Therefore, according to the ECHA guidance (2017), PPD is classified as a GHS Category 1 respiratory sensitizer. PPD is also listed as a Category 1 respiratory sensitizer by GHS Japan. PPD has a long history of respiratory sensitization reactions in fur and hair dyeing workers. However, there is no data to subclassify PPD to Category 1A (high potency, High score) or 1B (low potency, Moderate score). As the asthma-like symptoms seen in these workers cannot conclusively be linked to PPD exposure alone, as determined by MAK (2000), and the frequency of occurrence in humans could not be determined, a score of Moderate was assigned with low confidence.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *M*

PPD was assigned a score of Moderate for skin irritation/corrosivity based on ToxServices classifying it to GHS Category 3. GreenScreen® criteria classify chemicals as a Moderate hazard for skin irritation/corrosivity when they are classified to GHS Category 3 (CPA 2018b). The confidence in the score is low as PPD was not tested up to 100% and OECD Guideline 439 does not allow the classification as a mild skin irritant (GHS Category 3).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2024a (The authors of the ECHA dossier identified more studies for skin irritation; however, only the Key and/or GLP and guideline equivalent studies were included due to their higher reliability and adequacy in evaluating this endpoint.)
  - PPD (purity noted as Fisher Scientific Co. Certified Grade) was not irritating when 0.05 mL of 3% or 30% PPD in distilled water was applied to the shaved, intact skin of male albino guinea pigs (n=10) for 48 hours under open conditions. The overall irritation scores, mean erythema scores at 24/48/72h and mean edema scores at 24/48/72h for all animals exposed to 3% and 30% PPD were 0. No animals showed any signs of irritation (Klimisch 2, reliable with restrictions).
  - In a GLP-compliant, EPA OPP 81-6 study, male Dunkin-Harley guinea pigs (n=10) received topical applications of 3% and 30% (w/v) PPD (purity unspecified) in acetone:dimethyl phthalate (1:9 ratio) to the shaved skin for 48 hours under open conditions. The overall irritation scores for all animals at 3% and 30% PPD and time points 24 and 48 hours were 0. The study authors concluded 3% and 30% PPD was not irritating to the skin of guinea pigs (Klimisch 1, reliable without restriction).
- Chemical Book 2023, Cameo Chemicals 2024
  - PPD (50 g/L in water) has a pH of 9 at 20°C.
  - PPD is the strongest of the weak aromatic bases (NTP 1992).
- ECHA 2024c, CIR 2023
  - <u>*Surrogate: PPD Sulfate (CAS #16245-77-5 / 50994-40-6)*</u>: In a GLP-compliant *in vitro* human reconstructed epidermis study using the EpiSkin model according to OECD Guideline 439, neat PPD sulfate (purity not specified) was predicted to be not irritating. The

relative mean tissue viability of the test substance was 94%, which is > 50%; therefore, the study authors concluded PPD was non-irritating to the skin and did not warrant classification under GHS as a skin irritant (Klimisch 1, reliable without restriction).

- ECHA 2024c
  - *Surrogate: PPD Sulfate (CAS #16245-77-5 / 50994-40-6)*: PPD sulfate (1% w/v dispersion solution, purity not specified) had a measured pH of 2.33 at 29°C in an OECD Guideline 122 Determination of pH, Acidity, and Alkalinity study (GLP unspecified). The study authors concluded PPD sulfate is acidic (Klimisch 1, reliable without restriction).
- CIR 2023
  - PPD was at most mildly irritating to the skin of guinea pigs and rabbits in numerous irritation studies that tested concentrations up to 25%.
  - In a range-finding test in Dunkin-Hartley guinea pigs, the study authors concluded 70% PPD was a moderate skin irritant.
- SCCP 2006, SCCS 2012
  - A 2.5% PPD aqueous solution with 0.05% sodium sulfite was a mild dermal irritant when applied to abraded or intact rabbit skin; the primary irritation index was approximately 0.8 out of 8.
- AICIS 2014
  - In rabbits, 450 mg/kg PPD induced erythema and edema; however, no further details were reported, including irritation scores.
  - In another study in rabbits, 500 mg/kg PPD did not elicit irritation to the skin. No further details were provided.
- Based on the weight of evidence, a score of Moderate was assigned. All the studies available for PPD itself were conducted with dilution. Concentrations of up to 30% were not irritating (not classified under GHS) in animals based on reliable data. However, a 70% solution of PPD was reported as a moderate skin irritating in guinea pigs in a study with limited reported details. The surrogate PPD sulfate was negative in an OECD Guideline 439 study, which indicates it is either GHS not classified, or GHS Category 3 (UN 2023). PPD sulfate has a pH of 2.23, highly acidic, while PPD has a pH of approximately 9, weakly basic, indicating that PPD sulfate is expected to have higher skin irritation potential based on its more extreme pH. Therefore, the negative results in the *in vitro* OECD Guideline 439 study for PPD sulfate provided supporting evidence that PPD did not warrant classification as GHS Categories 1 or 2. Therefore, based on the qualitative description of "moderate" irritation with PPD in guinea pigs, ToxServices conservatively classified PPD to GHS Category 3.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): H

PPD was assigned a score of High for eye irritation/corrosivity based on the EU harmonized GHS Category 2A classification, supported by an OECD Guideline 405 equivalent study in rabbits with neat PPD. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified to GHS Category 2A (CPA 2018b). The confidence in the score is high as it is based on an authoritative A list.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU – GHS (H-statements) Annex 6 Table 3-1 – H319 – Causes serious eye irritation [Serious eye damage/eye irritation – Category 2A].
  - *Screening:*
    - GHS New Zealand – Eye irritation Category 2.

        - Based on its association with R phrase R36 from company data [H319 – Causes serious eye irritation] (CCID 2024).
    - GHS Japan – H320 – Causes eye irritation [Serious eye damage/eye irritation – Category 2B].
        - Based on a Draize test in rabbits administered undiluted test substance and resulting in an irritation score of 17 (out of 110) in addition to another test in which 30 mg of PPD was instilled into the eyes of rabbits resulting in redness and edema that resolved within 7 days (NITE 2011).
    - GHS – Australia – H319 – Causes serious eye irritation [Serious eye damage/eye irritation – Category 2A].
    - GHS Korea – H319 – Causes serious eye irritation [Serious eye damage/eye irritation – Category 2A].
    - GHS Malaysia – H319 – Causes serious eye irritation [Serious eye damage/eye irritation – Category 2A].
- ECHA 2024a (The authors of the ECHA dossier identified more studies for eye irritation; however, only the Key, GLP, and guideline equivalent study was included due to its higher reliability and adequacy in evaluating this endpoint.)
    - PPD was moderately irritating in an ocular irritation test conducted in a manner similar to OECD Guideline 405 (GLP unspecified). Male albino rabbits (n=2) were instilled with 10 mg solid PPD (purity 99.5%) into both eyes for 20 minutes after which one eye was washed with tap water for one minute and the other eye was left unwashed. Generalized slight corneal cloudiness, moderate iritis, and moderate conjunctivitis were reported for the unwashed eyes of the rabbits, and generalized slight corneal cloudiness, moderate iritis, and mild conjunctivitis was reported for the washed eyes. All irritative effects were resolved within 14 days post-treatment. However, no individual mean scores were provided for the irritation endpoints at any timepoint. The study authors concluded PPD was moderately irritating to the eye (Klimisch 2, reliable with restrictions). *Although no scores were provided for this study, the results of this study would qualitatively support a GHS Category 2A classification based on moderate irritation to the iris and conjunctivae, which are fully reversible within an observation period of 21 days (UN 2023).*
        - ToxServices notes this study is identified as conducted in accordance with OECD Guideline 405 by CIR (2023).
- CIR 2023
    - Additional studies found formulations containing up to 5% PPD to be at most weakly irritating to the eyes of guinea pigs and rabbits.
    - An ocular irritation study in rats (10/dose) exposed to formulations containing 5, 10, or 15% PPD reported keratitis and corneal opacities; however, no further details were provided.
- SCCP 2006, SCCS 2012
    - A 2.5% PPD (purity not specified) aqueous solution with 0.05% sodium sulfite was not an ocular irritant when instilled in rabbit eyes (n=3) and rinsed after 10 seconds; there was minimal conjunctival irritation in one animal.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): vH

PPD was assigned a score of Very High for acute aquatic toxicity based on the EU harmonized GHS Category 1 classification, the measured L/EC_{50} values as low as 0.066 – 3.9 mg/L in fish, 0.15 mg/L in daphnia, and 0.088 – 0.496 mg/L in algae in guideline studies. GreenScreen® criteria classify chemicals

as a Very High hazard for acute aquatic toxicity when acute toxicity values are ≤ 1 mg/L and when they are classified to GHS Category 1 (CPA 2018b). The confidence in the score is high based on an authoritative A list and on reliable, guideline studies for the target chemical for all three trophic levels.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU – GHS (H-statements) Annex 6 Table 3-1 – H400 – Very toxic to aquatic life [Hazardous to the aquatic environment (acute) – Category 1].
    - *Screening:*
        - GHS New Zealand – Hazardous to the aquatic environment – Acute Category 1.
            - Based on its association with the R Phrase R50/53 from company data [H400: Very toxic to aquatic life] (CCID 2024).
        - GHS Japan – H400 – Very toxic to aquatic life [Hazardous to the aquatic environment (acute) – Category 1].
            - Based on an LC_{50} = 0.066 mg/L for fish (*Oryzias latipes*) (NITE 2011).
        - GHS Korea – H400 – Very toxic to aquatic life [Hazardous to the aquatic environment (acute) – Category 1].
        - GHS Malaysia – H400 – Very toxic to aquatic life [Hazardous to the aquatic environment (acute) – Category 1].
- ECHA 2024a (The authors of the ECHA dossier identified more studies for acute aquatic toxicity for fish, crustacea, and algae; however, only the GLP and guideline studies were included due to their higher reliability and adequacy in evaluating this endpoint).
    - 96-hr LC_{50} mortality (*Oncorhynchus mykiss*, Rainbow trout) = 3.9 mg/L measured (not specified) (purity ≥ 98%, GLP-compliant, equiv. to OECD Guideline 203) (Klimisch 1, reliable without restriction).
    - 96-hr LC_{50} mortality (*O. latipes*, fish) = 0.066 mg/L measured (time weighted average (TWA)) (purity 98%, GLP-compliant, OECD Guideline 203) (Klimisch 2, reliable with restrictions).
    - 48-hr EC_{50} mobility (*Daphnia magna*) = 0.15 mg/L measured (mean. arith) (purity > 98%, GLP-compliant, EPA OTS 797.1300) (Klimisch 2, reliable with restrictions).
    - 48-hr EC_{50} mobility (*D. magna*) = 0.33 mg/L measured (time weighted average (TWA)) (purity 98%, GLP-compliant, OECD Guideline 202) (Klimisch 2, reliable with restrictions).
    - 48-hr EC_{50} mobility (*D. magna*) = 0.496 mg/L measured (geom. mean) (purity not specified, GLP-compliant, OECD Guideline 202) (Klimisch 2, reliable with restrictions).
    - 72-hr EC_{50} growth rate (*Raphidocelis subcapitata*) = 0.478 mg/L measured (TWA), 72-hr EC_{50} biomass = 0.089 mg/L measured (TWA), 72-hr EC_{50} yield = 0.088 mg/L measured (TWA) (purity 98%, GLP-compliant, OECD Guideline 201) (Klimisch 2, reliable with restrictions).
    - 72-hr EC_{50} growth rate (*R. subcapitata*) = 0.27 mg/L measured (TWA), 72-hr EC_{50} biomass = 0.056mg/L measured (TWA) (purity not specified, GLP-compliant, OECD Guideline 201) (Klimisch 2, reliable with restrictions).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): vH

PPD was assigned a score of Very High for chronic aquatic toxicity based on the measured NOEC values as low as 0.00414 mg/L in daphnia and < 0.029 mg/L in algae. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when chronic toxicity values are ≤ 0.1 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data fro two trophic levels sufficient to assign the highest hazard score.

- Authoritative and Screening Lists

  - *Authoritative:*
    - EU – GHS (H-statements) Annex 6 Table 3-1 – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
  - *Screening:*
    - GHS New Zealand – Hazardous to the aquatic environment – Chronic Category 1.
      - Based on its association with the R Phrase R50/53 from company data [H410 – Very toxic to aquatic life with long lasting effects] (CCID 2024).
    - GHS Australia – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS Malaysia – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS – Korea – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS Japan – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
      - Based on not rapidly degradable and 21-day NOEC of 0.043 mg/L for crustacea (NITE 2011).

- ECHA 2024a (The authors of the ECHA dossier identified additional studies for chronic aquatic toxicity for crustacea and algae; however, only the GLP and guideline studies were included due to their higher reliability and adequacy in evaluating this endpoint).
  - 21-day NOEC reproduction (*D. magna*) = 50 mg/L measured (TWA), 21-NOEC reproduction = 12.5 mg/L nominal (purity not specified, GLP-compliant, OECD Guideline 211) (Klimisch 1, reliable without restriction).
  - 21-day NOEC reproduction and length (mm) (*D. magna*) = 0.589 µg/L (equiv. to 5.89×10^{-4} mg/L) measured (geom. mean), 21-NOEC reproduction = 4.14 µg/L (equiv. to 0.00414 mg/L) measured (geom. mean), 21-NOEC immobilization = 105 µg/L (equiv. to 0.105 mg/L) measured (geom. mean), maximum acceptable toxicant concentration (MATC) = 1.56 µg/L (equiv. to 0.00156 mg/L) (purity > 98%, GLP-compliant, EPA OTS 797.1330) (Klimisch 2, reliable with restrictions).
  - 21-day NOEC and LOEC reproduction (*D. magna*) = 0.043 and 0.072 mg/L, respectively, measured (TWA) (purity 98%, GLP-compliant, OECD Guideline 211) (Klimisch 2, reliable with restrictions).
  - 72-hr NOEC growth rate (*R. subcapitata*) = 56 mg/L nominal, 72-hr NOEC biomass = 32 mg/L nominal (purity 99.5%, GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).
  - 72-hr NOEC (*Desmodesmus subspicatus*) = 6.47 mg/L measured (purity not specified, GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).
  - 72-hr NOEC growth rate, measured, and yield (*R. subcapitata*) = 0.008 mg/L measured (TWA) (purity 98%, GLP-compliant, OECD Guideline 201) (Klimisch 2, reliable with restrictions).
  - 72-hr NOEC growth rate and biomass (*R. subcapitata*) < 0.029 mg/L measured (TWA), 72-hr EC_{10} growth rate = 0.071 mg/L measured (TWA), 72-hr EC_{10} biomass = 0.014 mg/L measured (TWA) (purity not specified, GLP-compliant, OECD Guideline 201) (Klimisch 2, reliable with restrictions).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *H*

PPD was assigned a score of High for persistence based on an estimated half-life of 75 days in its predicted major compartment, soil. GreenScreen® criteria classify chemicals as a High hazard for persistence when partitioning occurs mainly to soil or sediment and the half-life is > 60 to 180 days in these compartments (CPA 2018b). The confidence in the score is low due to dependence on modeling.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU – GHS (H-statements) Annex 6 Table 3-1 – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
  - *Screening:*
    - GHS New Zealand – Hazardous to the aquatic environment – Chronic Category 1.
      - Based on its association with the R Phrase R50/53 from company data [H410 – Very toxic to aquatic life with long lasting effects] (CCID 2024).
    - GHS Australia – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS Malaysia – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS – Korea – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
    - GHS Japan – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 1].
      - Based on not rapidly degradable and 21-day NOEC of 0.043 mg/L for crustacea (NITE 2011).
- ECHA 2024a
  - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 D (closed bottle test) was performed with activated sludge (adaptation not specified) exposed to PPD (purity not specified) at 2 mg/L for 84 days. At 28 days with and without silica, the level of degradation (BOD/ThOD) was 28% with silica and 30% without silica. The study authors concluded that PPD was not inhibitory to the inoculum based on a lack of reduction in the endogenous respiration, the similar degradation levels with and without silica indicate that PPD is not toxic to the activated sludge, and, overall, PPD is not readily biodegradable (Klimisch 2, reliable with restrictions).
  - A non-GLP-compliant inherent biodegradability test conducted according to OECD Guideline 302 A (Modified SCAS test) was performed with industrial activated sludge (adaptation not specified) exposed to PPD (purity not specified) at 15 mg/L for 29 days. A slight reduction in non-purgeable organic carbon (NPOC) was found in primary settled sewage indicated PPD was inhibitory to the activated sludge at a concentration of 15 mg/L. A high removal percentage or 47% was reported on day one, which the study authors attributed to dilution/adsorption. For the remaining of the test period, the removal decreased to 0% and remained 0% up to day 29. Therefore, the study authors concluded no biodegradation was observed and the removal of PPD in wastewater treatment plants is very unlikely (Klimisch 2, reliable with restrictions).
  - The authors of the ECHA dossier concluded that biodegradation is not the primary route of degradation of PPD.

  - In a GLP-compliant indirect photolysis screening test: sunlight photolysis in waters containing Dissolved Humic Substances conducted according to EPA OTS 795.70, PPD (99.72% purity) had an overall half-life in synthetic humic water of less than an hour, and was considered photolabile. The photolysis half-life was 0.12 days (equivalent to 56 minutes). Overall, the study authors concluded PPD was very photolabile via both direct and indirect photolysis.
- HSDB 2019
  - PPD is rapidly degradable in surface water via abiotic degradation by photochemically produced peroxy radicals with a half-life of 1 day.
  - PPD is not expected to volatize from dry soil surfaces or adhere to sediment in water based on an estimated Koc of 16. It is not expected to volatilize from moist soil surfaces based on an estimated Henry's Law constant of $6.7x10^{-10}$ atm-m^3/mol.
  - In the air, PPD degrades via oxidative and photolytic mechanisms.
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that PPD is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 74.6% will partition to soil with a half-life of 75 days, 25.3% will partition to water with a half-life of 37.5 days, 0.0889% will partition to sediment with a half-life of 337.5 days, and $7.97x10^{-3}$% will partition to air with a half-life of 1.46 hours (Appendix F).
- Based on the weight of evidence, a score of High was assigned. PPD was not readily or inherently biodegradable in OECD Guideline 301 D and 302A tests. The authors of the ECHA dossier indicated that biodegradation was not PPD's primary route of degradation. Instead, in an EPA OTS 795.70 indirect photolysis screening test, PPD is rapidly degradable in water with a half-life of less than an hour via direct and indirect photolysis. Additionally, PPD is expected to degrade rapidly in the air via oxidative and photolytic mechanisms (ECHA 2024a, HSDB 2019). However, the degradation products were not identified, and the fast abiotic processes likely only represent primary degradation. Primary degradation could only be used to support rapid degradability under GHS except when the degradation products are not hazardous to the environment (UN 2023). Chronic aquatic toxicity studies with PPD indicate that the aquatic degradation products of PPD may be highly aquatically toxic. Therefore, ToxServices relied on modeled half-life of 75 days for its primary compartment, soil, to assign a High score for this endpoint.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL

PPD was assigned a score of Very Low for bioaccumulation based on its measured log K_{ow} of -0.84 and modeled BCFs of 0.8973 and 3.162. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the BCF/BAF is ≤ 100 and when log K_{ow} is ≤ 4 (CPA 2018b). The confidence in the score is high as it is based in part on measured log K_{ow} data on the target chemical, with support from modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2024a
  - PPD has a log K_{ow} value of -0.84 at 20ºC as identified in an OECD Guideline 107 test (Klimisch 1, reliable without restriction).
- U.S. EPA 2017
  - BCFBAF predicts a BCF of 3.162 using the regression based model based on a measured log K_{ow} of -0.84, and a BCF of 0.8973 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix F).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
PPD was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score was low as it was not based on an authoritative list or measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2024a
  - PPD is not explosive based on a lack of functional groups related to explosion hazards as well as calculated thermodynamic properties (Klimisch 1, reliable without restriction).
  - PPD is not oxidizing based on a lack of functional groups related to oxidation hazards as well as calculated thermodynamic properties and negative oxygen balance (Klimisch 1, reliable without restriction).
  - PPD (purity 98.3%) did not ignite on contact with air in an EU Method A.10 flammability test (Klimisch 1, reliable without restriction).
- ILO 1997
  - Finely dispersed particles form explosive mixtures with air. Additionally, the risk of fire and explosion may occur on contact with strong oxidizing agents.
- NITE 2006, 2011
  - National Institute of Technology (NITE) (2006) reports PPD is classified as flammable and as Hazard Class Division 6.1, UN #1673, Packaging Group 3 as the rationale for a GHS Not Classified classification for self-heating and flammable solids. NITE (2011) did not classify PPD as a reactive chemical.
- HSDB 2019
  - The fine powder is a significant dust explosion hazard with a minimum explosive concentration of 0.025 g/L.
- Sigma Aldrich 2023
  - A safety data sheet (SDS) for *p*-phenylenediamine (≥ 99% purity) indicates that strong heating should be avoided as the substance forms explosive mixtures with air upon intense heating at a range of 368.15 – 383.15 K (equivalent to 95-110°C). However, PPD is chemically stable under standard ambient conditions (room temperature). Additionally, the SDS indicates PPD reacts violently with strong oxidizing agents.
- Based on the weight of evidence, ToxServices concluded PPD as not reactive. PPD is not self-heating with a melting point of 142°C (which is ≤ 160°C) under standard pressure and it did not ignite upon contact with air indicating it is not pyrophoric. It is not expected to be explosive or self-reactive based on chemical structure. PPD has no reactive functional groups that would make it oxidizing or explosive, and it is not a peroxide. As it is not explosive, it does not require desensitization. It is stable under recommended storage conditions. When PPD particulate is mixed with the air and heated, an increased risk of explosion of PPD may occur. However, this is not typically evaluated under the explosiveness endpoint of GHS. Overall, PPD is GHS Not Classified for reactivity (UN 2023). No data were found regarding corrosivity to metal.

Flammability (F) Score (vH, H, M, or L): L
PPD was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable solid under GHS criteria based on results of flammability tests with the target chemical.

GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is available (CPA 2018b). The confidence in the score is high as it is based on experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2024a
  - PPD (purity 98.3%) was not flammable in an EU Method A.10 flammability test with no ignition achieved during the full 2 minutes of heating (Klimisch 1, reliable without restriction).
- ILO 1997
  - The International Labour Organization (ILO) reports PPD is classified as combustible.
- Based on the flammability test result, ToxServices did not classify PPD as a flammable solid under GHS criteria (UN 2023).

Use of New Approach Methodologies (NAMs)[9] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for respiratory sensitization, persistence, and bioaccumulation, and *in vitro* testing for genotoxicity and endocrine activity. NAMs are non-animal alternatives that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 2020). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

As shown in Table 4, Type I (input data) uncertainties in PPD's NAMs dataset include no or insufficient experimental data for endocrine activity and respiratory sensitization, and lack of established test methods for respiratory sensitization. PPD's Type II (extrapolation output) uncertainties include lack of defined applicability domains OECD QSAR Toolbox in examination of structural alerts, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in vitro* receptor binding activity assays, the limitation of the OECD Guideline 439 *in vitro* skin irritation assay in identifying GHS Category 3 mild skin irritants, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of PPD's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Endocrine activity:** No *in vivo* data are available on circulating hormone levels. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[10]. The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal

[9] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

[10] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

	aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[11]. **Endocrine activity:** The *in vivo* relevance of EDSP Tox 21 screening assays is unknown due to lack of consideration of metabolism and other toxicokinetic factors. EDSP Tox 21 assays do not cover all critical endocrine pathways. **Skin irritation**: OECD Guideline 439 test is only used to identify irritating substances (GHS Category 2) and non-irritating substances (no category), and does not allow the classification as a mild skin irritant (GHS Category 3)[12]. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.

Endpoint	NAMs Data Available and Evaluated? (Y/N)	Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	Y	*In vitro* test: OECD Guideline 439 Test
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™

[11] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[12] https://www.oecd-ilibrary.org/docserver/9789264242845-en.pdf?expires=1614097324&id=id&accname=guest&checksum=D664A7EDCDE297919BE9A478941EBEC6

		Non-animal testing: OECD 301 D and 302 A Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for PPD (CAS #106-50-3)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	PPD	106-50-3	M	L	*M*	*M*	*M*	H	*vH*	H	*vH*	DG	H	*M*	*M*	H	vH	vH	*H*	vL	*L*	L

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	Yes	No	Yes	Yes	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
PPD	2

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

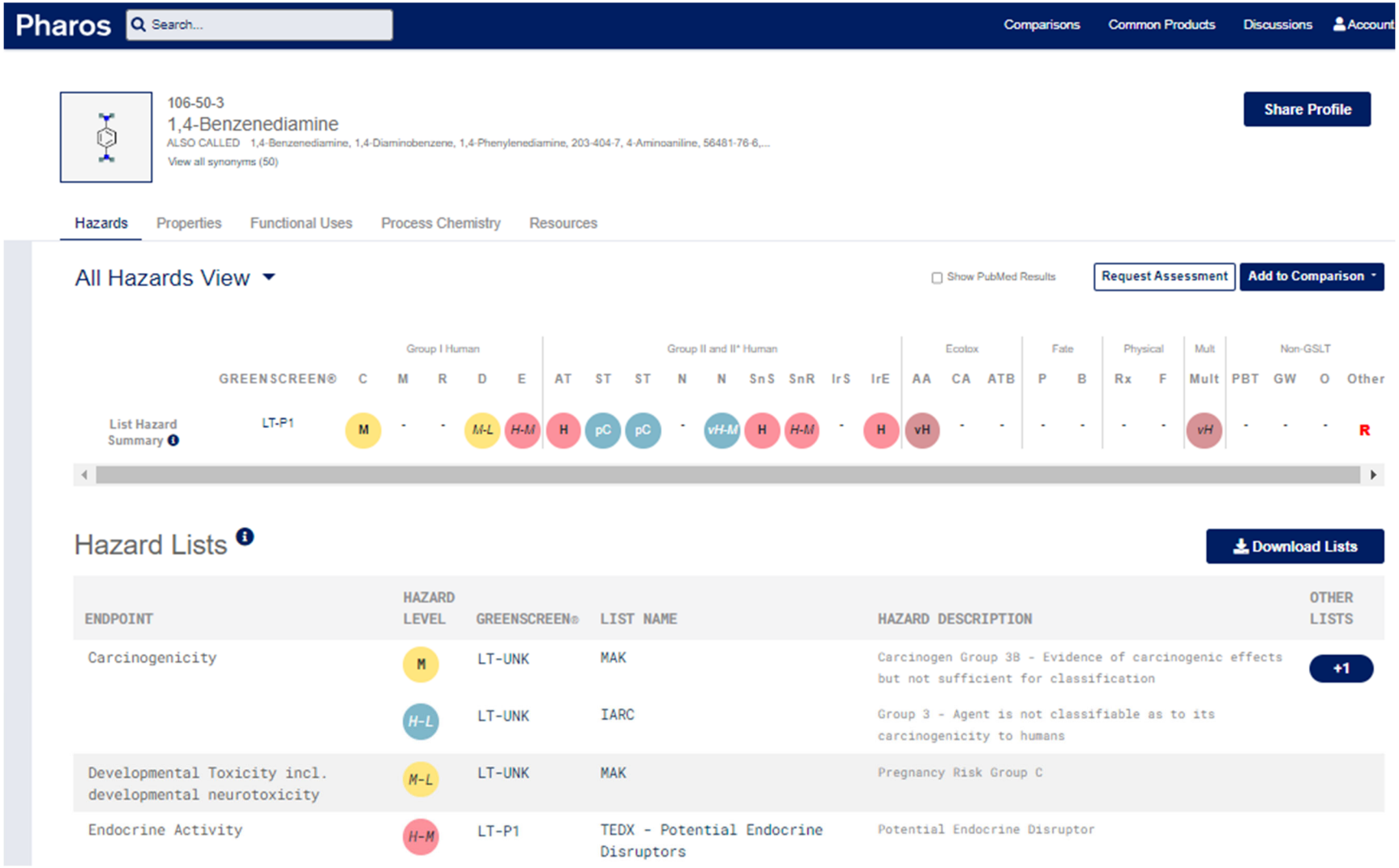
Chemical Name	Final GreenScreen® Benchmark Score
PPD	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for PPD (CAS #106-50-3)



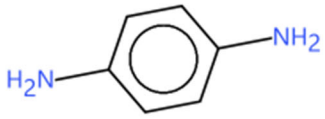
Acute Mammalian Toxicity	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H311 - Toxic in contact with skin [Acute toxicity (dermal) - Category 3]	+19
	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H301 - Toxic if swallowed [Acute toxicity (oral) - Category 3]	
	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H331 - Toxic if inhaled [Acute toxicity (inhalation) - Category 3]	
	vH	LT-UNK	GHS - Malaysia	H300 - Fatal if swallowed [Acute toxicity (oral) - Category 1 or 2]	
	vH-H	LT-UNK	GHS - Australia	H331 - Toxic if inhaled [Acute toxicity (inhalation) - Category 3]	
	vH-H	LT-UNK	GHS - Malaysia	H331 - Toxic if inhaled [Acute toxicity (inhalation) - Category 3]	
	H	LT-UNK	GHS - Australia	H311 - Toxic in contact with skin [Acute toxicity (dermal) - Category 3]	
	H	LT-UNK	GHS - Korea	H301 - Toxic if swallowed [Acute toxicity (oral) - Category 3]	
	H	LT-UNK	GHS - Korea	H311 - Toxic in contact with skin [Acute toxicity (dermal) - Category 3]	
	H	LT-UNK	GHS - Korea	H331 - Toxic if inhaled [Acute toxicity (inhalation) - Category 3]	
	H	LT-UNK	GHS - Malaysia	H311 - Toxic in contact with skin [Acute toxicity (dermal) - Category 3]	
	H	LT-UNK	GHS - New Zealand	Acute dermal toxicity category 3	
	H	LT-UNK	GHS - New Zealand	Acute inhalation toxicity category 3	
	H	LT-UNK	GHS - New Zealand	Acute oral toxicity category 3	
	H	LT-UNK	GHS - Australia	H301 - Toxic if swallowed [Acute toxicity (oral) - Category 3]	
	H	LT-UNK	GHS - Japan	H301 - Toxic if swallowed [Acute Toxicity (oral) - Category 3]	
	H	LT-UNK	GHS - Japan	H331 - Toxic if inhaled [Acute toxicity (inhalation: dust, mist) - Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H301 - Toxic if swallowed (unverified) [Acute toxicity (oral) - Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H311 - Toxic in contact with skin (unverified) [Acute toxicity (dermal) - Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H331 - Toxic if inhaled (unverified) [Acute toxicity (inhalation) - Category 3]	

Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H370 - Causes damage to organs (unverified) [Specific target organ toxicity - single exposure - Category 1]	
Systemic Toxicity/Organ Effects incl. immunotoxicity-Repeated Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H373 - May cause damage to organs through prolonged or repeated exposure (unverified) [Specific target organ toxicity - repeated exposure - Category 2]	
Neurotoxicity-Repeated Exposure	vH-M	LT-UNK	G&L - Neurotoxic Chemicals	Neurotoxic	
Skin Sensitization	H	LT-UNK	MAK	Sensitizing Substance Sh - Danger of skin sensitization	+6
	H-M	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	
	H-M	LT-UNK	GHS - Korea	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	
	H-M	LT-UNK	GHS - Malaysia	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	
	H	LT-UNK	GHS - New Zealand	Skin sensitisation category 1	
	H-M	LT-UNK	GHS - Australia	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H317 - May cause an allergic skin reaction (unverified) [Skin sensitization - Category 1]	
Respiratory Sensitization	H-M	LT-UNK	GHS - Japan	H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled [Respiratory sensitizer - Category 1]	+4
	H	NoGS	CHE - Toxicant Database	Asthma - allergen, sensitizer - strong evidence	
	M	NoGS	Quebec CSST - Asthma Agents	Agent Causing Occupational Asthma	
	M	NoGS	AOEC - Asthmagens	Suspected asthmagen (R) - but does not meet AOEC criteria)	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled (unverified) [Respiratory sensitization - Category 1]	

Eye Irritation/Corrosivity	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	+6
	H	LT-UNK	GHS - Korea	H319 - Causes serious eye irritation [Serious eye damage/irritation - Category 2]	
	H	LT-UNK	GHS - Australia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - Malaysia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - New Zealand	Eye irritation category 2	
	M	NoGS	GHS - Japan	H320 - Causes eye irritation [Serious eye damage/eye irritation - Category 2B]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	
Acute Aquatic Toxicity	vH	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H400 - Very toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 1]	+4
	vH	LT-UNK	GHS - Japan	H400 - Very toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 1]	
	vH	LT-UNK	GHS - Korea	H400 - Very toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 1]	
	vH	LT-UNK	GHS - Malaysia	H400 - Very toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H400 - Very toxic to aquatic life (unverified) [Hazardous to the aquatic environment (acute) - Category 1]	
Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	vH	LT-UNK	GHS - Japan	H370 - Causes damage to organs [Specific target organs/systemic toxicity following single exposure - Category 1]	
Systemic Toxicity/Organ Effects [Repeated Exposure] and/or Neurotoxicity [Repeated Exposure]	H	LT-UNK	GHS - Japan	H372 - Causes damage to organs through prolonged or repeated exposure [Specific target organs/systemic toxicity following repeated exposure - Category 1]	
Skin and/or Respiratory Sensitization	H-M	LT-UNK	GHS - Japan	H317 - May cause an allergic skin reaction [Skin Sensitization - Category 1A]	

T & P and/or B [(Chronic Aquatic Toxicity and sometimes Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	H	LT-UNK	GHS - Malaysia	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	+1
	U	LT-P1	GHS - Japan	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	vH	LT-UNK	GHS - New Zealand	Hazardous to the aquatic environment - acute category 1	+5
	vH	LT-P1	GHS - New Zealand	Hazardous to the aquatic environment - chronic category 1	
	U	LT-P1	EU - GHS (H-Statements) Annex 6 Table 3-1	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	
	U	LT-P1	GHS - Australia	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	
	U	LT-P1	GHS - Korea	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H410 - Very toxic to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 1]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-P1	German FEA - Substances Hazardous to Waters	Class 3 - Severe Hazard to Waters	

APPENDIX D: OECD Toolbox Profiling Results for PPD (CAS #106-50-3)

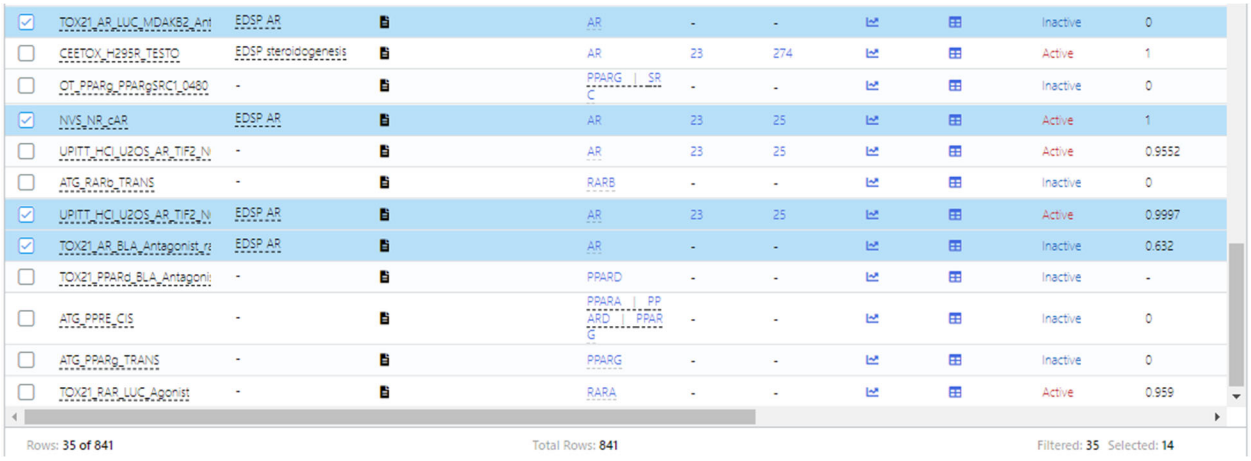
Filter endpoint tree...	1 [target]
Structure	
Structure info	
Additional Ids	EC Number:2034047
CAS Number	106-50-3
CAS-SMILES relation	High
Chemical name(s)	1,4-Benzenediamine
Identity	Sources:41
Molecular formula	C6H8N2
Predefined substance type	Mono constituent
SMILES	Nc1ccc(N)cc1
Parameters	
Physical Chemical Properties	
Environmental Fate and Transport	
Ecotoxicological Information	
Human Health Hazards	
Profiling	
Predefined	
Database Affiliation	Acute Oral toxicity DB
Inventory Affiliation	AIIC
OECD HPV Chemical Categories	Not categorized
Substance type	Discrete chemical
US-EPA New Chemical Categories	Anilines (Acute toxicity)
Endpoint Specific	
Carcinogenicity (genotox and nongenotox) alerts by ISS	Primary aromatic amine,hydroxyl amine and its derived esters (Genotox)
Respiratory sensitisation	Pro-Michael Addition
Metabolism/Transformation	
Hydrolysis simulator (acidic)	0 metabolite(s)
Hydrolysis simulator (basic)	0 metabolite(s)
Hydrolysis simulator (neutral)	0 metabolite(s)

APPENDIX E: CompTox EDSP21 Results for PPD (CAS #106-50-3)

Name	Assay Lists	Details	SeqAPASS	Gene Symbol	AOP	Event	Repr. Plot	All Plots	Hit Call	Continuous Hit Call	Top
				ESR							
ATG_ERE_CIS	EDSP ER			ESR1	-	-			Inactive	0	-0.01
OT_ERa_GFPERaERE_0480	EDSP ER			ESR1	-	-			Active	0.9993	49.48
NVS_NR_bER	EDSP ER		NP_001001443.1	ESR1	-	-			Inactive	0	3.55
TOX21_ERR_Antagonist	-		NP_004442.3	ESRRA	-	-			Inactive	0	0.03
NVS_NR_mERa	EDSP ER			Esr1	-	-			Inactive	0.0223	0
TOX21_PGC_ERR_Antagonist	-		NP_004442.3	ESRRA	-	-			Inactive	0.0253	26.53
OT_ER_ERaERb_1440	EDSP ER		NP_000116.2 NP_001428.1	ESR1 | ESR2	-	-			Active	1	172.68
TOX21_ERa_BLA_Agonist_ratio	EDSP ER			ESR1	-	-			Inactive	-	0.04
TOX21_ERa_LUC_VM7_Antago	-			ESR1	-	-			Inactive	0	9.89
NVS_NR_hER	EDSP ER			ESR1	-	-			Inactive	0	0
OT_ER_ERbERb_1440	EDSP ER		NP_001428.1	ESR2	-	-			Active	1	67.16
TOX21_ERR_Agonist	-			ESRRA	-	-			Inactive	0	0.61
OT_ER_ERbERb_0480	EDSP ER			ESR2	-	-			Inactive	0.6462	22.21
OT_ER_ERaERa_0480	EDSP ER			ESR1	-	-			Inactive	0	0
TOX21_ERa_LUC_VM7_Antago	EDSP ER			ESR1	-	-			Inactive	0	0.87
ACEA_ER_80hr	EDSP ER			ESR1	220	1394			Inactive	0	0
TOX21_PGC_ERR_Agonist	-			ESRRA	-	-			Active	0.9996	40.28
CEETOX_H295R_ESTRONE	EDSP steroidogenesis			ESR1 | ESR2	-	-			Inactive	0.0001	0.63
ATG_ERRg_TRANS	-			ESRRG	-	-			Inactive	0	0
ATG_ERRa_TRANS	-			ESRRA	-	-			Inactive	0	0
ATG_ERa_TRANS	EDSP ER			ESR1	-	-			Inactive	0	0.54
TOX21_ERb_BLA_Antagonist_r	-			ESR2	-	-			Active	0.9979	44.64
TOX21_ERa_LUC_VM7_Agonis	EDSP ER			ESR1	-	-			Inactive	-	0
OT_ER_ERaERb_0480	EDSP ER			ESR1 | ESR2	-	-			Inactive	0	12.52
TOX21_ERa_BLA_Antagonist_r	EDSP ER			ESR1	-	-			Inactive	0	0
TOX21_ERa_LUC_VM7_Agonis	-		NP_000116.2	ESR1	-	-			Inactive	-	0.66
OT_ERa_GFPERaERE_0120	EDSP ER			ESR1	-	-			Active	1	36.13
TOX21_ERb_BLA_Agonist_ratio	-			ESR2	-	-			Inactive	-	0.02
OT_ER_ERaERa_1440	EDSP ER			ESR1	-	-			Inactive	0	7.92
CEETOX_H295R_ESTRADIOL	EDSP steroidogenesis			ESR1 | ESR2	-	-			Inactive	0.3635	1.09

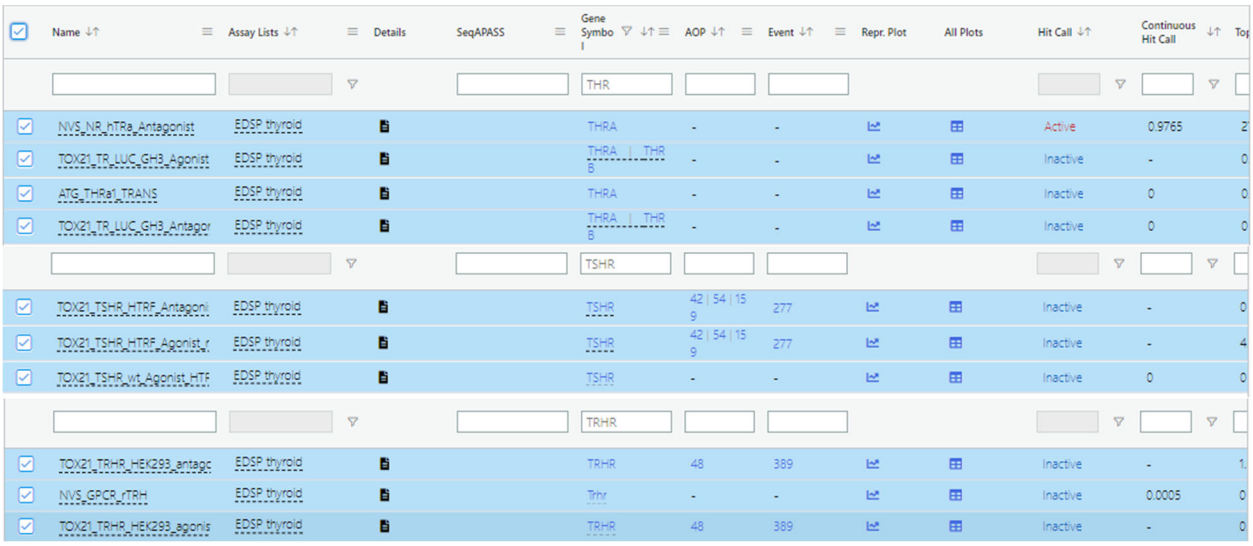
Rows: 30 of 841 Total Rows: 841 Filtered: 30 Selected: 18

Name	Assay Lists	Details	SeqAPASS	Gene Symbol	AOP	Event	Repr. Plot	All Plots	Hit Call	Continuous Hit Call	Top
				AR							
ATG_PPARd_TRANS	-			PPARD	-	-			Inactive	0	
TOX21_AR_BLA_Agonist_ratio	EDSP AR			AR	23	25			Inactive	0	
ATG_AR_TRANS	EDSP AR			AR	-	-			Inactive	0	
TOX21_PPARd_BLA_Agonist_r	-			PPARD	-	-			Inactive	-	
ATG_RARa_TRANS	-			RARA	-	-			Inactive	0	
ACEA_AR_agonist_80hr	-			AR	23 | 220	25 | 1394			Inactive	-	
TOX21_AR_LUC_MDAKB2_Ag	EDSP AR			AR	23	25			Inactive	-	
OT_AR_ARSRC1_0960	EDSP AR			AR | SRC	23	25			Inactive	0	
OT_AR_ARSRC1_0480	EDSP AR			AR | SRC	23	25			Inactive	0	
OT_AR_ARELUC_AG_1440	EDSP AR			AR	23	25			Inactive	0	
TOX21_AR_LUC_MDAKB2_Ant	EDSP AR			AR	-	-			Inactive	-	
UPITT_HCI_U2OS_AR_TIF2_N	EDSP AR			AR	23	25			Active	0.9992	

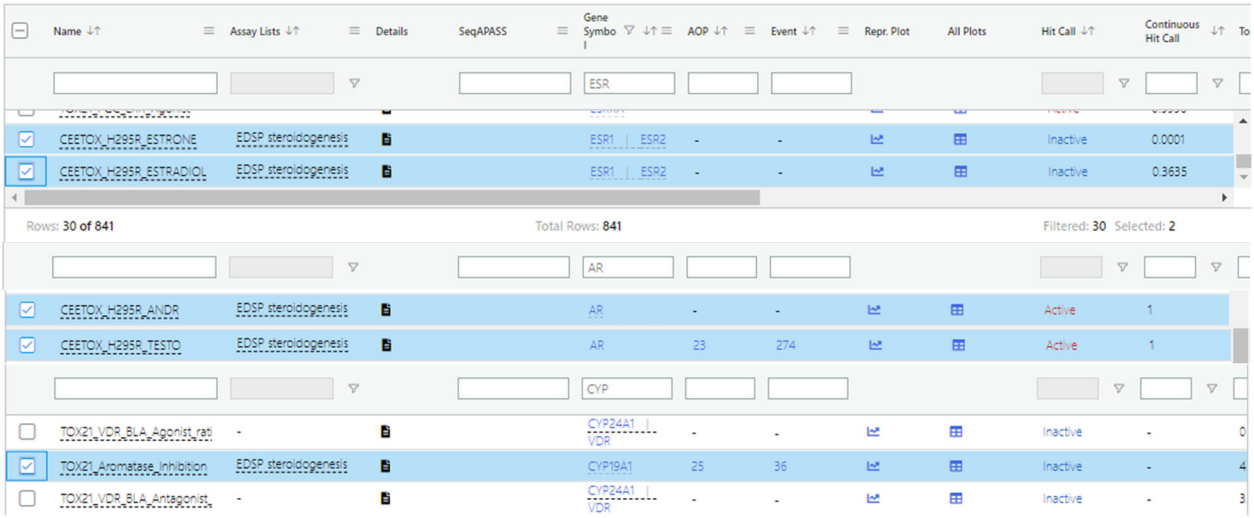


☑	TOX21_AR_LUC_MDAKB2_Ant	EDSP AR		AR	-	-		Inactive	0
☐	CEETOX_H295R_TESTO	EDSP steroidogenesis		AR	23	274		Active	1
☐	OT_PPARg_PPARgSRC1_0480	-		PPARG | SRC	-	-		Inactive	0
☑	NVS_NR_cAR	EDSP AR		AR	23	25		Active	1
☐	UPITT_HCI_U2OS_AR_TIF2_N	-		AR	23	25		Active	0.9552
☐	ATG_RARb_TRANS	-		RARB	-	-		Inactive	0
☑	UPITT_HCI_U2OS_AR_TIF2_N	EDSP AR		AR	23	25		Active	0.9997
☑	TOX21_AR_BLA_Antagonist_r	EDSP AR		AR	-	-		Inactive	0.632
☐	TOX21_PPARd_BLA_Antagoni	-		PPARD	-	-		Inactive	-
☐	ATG_PPRE_CIS	-		PPARA | PPARD | PPARG	-	-		Inactive	0
☐	ATG_PPARg_TRANS	-		PPARG	-	-		Inactive	0
☐	TOX21_RAR_LUC_Agonist	-		RARA	-	-		Active	0.959

Rows: 35 of 841 Total Rows: 841 Filtered: 35 Selected: 14



☑	Name	Assay Lists	Details	SeqAPASS	Gene Symbol	AOP	Event	Repr. Plot	All Plots	Hit Call	Continuous Hit Call
					THR						
☑	NVS_NR_hTRa_Antagonist	EDSP thyroid			THRA	-	-			Active	0.9765
☑	TOX21_TR_LUC_GH3_Agonist	EDSP thyroid			THRA | THRB	-	-			Inactive	-
☑	ATG_THRa1_TRANS	EDSP thyroid			THRA	-	-			Inactive	0
☑	TOX21_TR_LUC_GH3_Antagor	EDSP thyroid			THRA | THRB	-	-			Inactive	0
					TSHR						
☑	TOX21_TSHR_HTRF_Antagoni	EDSP thyroid			TSHR	42 | 54 | 159	277			Inactive	-
☑	TOX21_TSHR_HTRF_Agonist_r	EDSP thyroid			TSHR	42 | 54 | 159	277			Inactive	-
☑	TOX21_TSHR_wt_Agonist_HTF	EDSP thyroid			TSHR	-	-			Inactive	0
					TRHR						
☑	TOX21_TRHR_HEK293_antago	EDSP thyroid			TRHR	48	389			Inactive	-
☑	NVS_GPCR_rTRH	EDSP thyroid			Trhr	-	-			Inactive	0.0005
☑	TOX21_TRHR_HEK293_agonis	EDSP thyroid			TRHR	48	389			Inactive	-



☐	Name	Assay Lists	Details	SeqAPASS	Gene Symbol	AOP	Event	Repr. Plot	All Plots	Hit Call	Continuous Hit Call
					ESR						
☑	CEETOX_H295R_ESTRONE	EDSP steroidogenesis			ESR1 | ESR2	-	-			Inactive	0.0001
☑	CEETOX_H295R_ESTRADIOL	EDSP steroidogenesis			ESR1 | ESR2	-	-			Inactive	0.3635

Rows: 30 of 841 Total Rows: 841 Filtered: 30 Selected: 2

					AR						
☑	CEETOX_H295R_ANDR	EDSP steroidogenesis			AR	-	-			Active	1
☑	CEETOX_H295R_TESTO	EDSP steroidogenesis			AR	23	274			Active	1
					CYP						
☐	TOX21_VDR_BLA_Agonist_rat	-			CYP24A1 | VDR	-	-			Inactive	-
☑	TOX21_Aromatase_Inhibition	EDSP steroidogenesis			CYP19A1	25	36			Inactive	-
☐	TOX21_VDR_BLA_Antagonist_	-			CYP24A1 | VDR	-	-			Inactive	-

APPENDIX F: EPI Suite™ Modeling Results for PPD (CAS #106-50-3)

(Estimated values included in the GreenScreen® are highlighted and bolded)

CAS Number: 000106-50-3
SMILES : Nc(ccc(N)c1)c1
CHEM : 1,4-BENZENEDIAMINE
MOL FOR: C6 H8 N2
MOL WT : 108.14
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): -0.84
Boiling Point (deg C) : 274.00
Melting Point (deg C) : 142.00
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): 31000
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = -0.39
Log Kow (Exper. database match) = -0.30
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 253.58 (Adapted Stein & Brown method)
Melting Pt (deg C): 52.83 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.000504 (Modified Grain method)
VP (Pa, 25 deg C) : 0.0672 (Modified Grain method)
MP (exp database): 146 deg C
BP (exp database): 267 deg C
Subcooled liquid VP: 0.00767 mm Hg (25 deg C, Mod-Grain method)
: 1.02 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1.31e+005
log Kow used: -0.84 (user entered)
melt pt used: 142.00 deg C
Water Sol (Exper. database match) = 3.7e+004 mg/L (23 deg C)
Exper. Ref: SEIDELL,A (1941)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 41093 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Anilines (Unhindered)
Anilines (amino-para)

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:

Bond Method : 6.73E-010 atm-m3/mole (6.82E-005 Pa-m3/mole)
Group Method: 8.88E-010 atm-m3/mole (9.00E-005 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 2.313E-009 atm-m3/mole (2.344E-004 Pa-m3/mole)
VP: 0.000504 mm Hg (source: MPBPVP)
WS: 3.1E+004 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: -0.84 (user entered)
Log Kaw used: -7.560 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 6.720
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.2286
Biowin2 (Non-Linear Model) : 0.0878
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.6903 (weeks-months)
Biowin4 (Primary Survey Model) : 3.4750 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.1308
Biowin6 (MITI Non-Linear Model): 0.0626
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.1013
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 1.02 Pa (0.00767 mm Hg)
Log Koa (Koawin est): 6.720
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 2.93E-006
Octanol/air (Koa) model: 1.29E-006
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.000106
Mackay model : 0.000235
Octanol/air (Koa) model: 0.000103

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 176.3599 E-12 cm3/molecule-sec
Half-Life = 0.061 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 0.728 Hrs
Ozone Reaction:
No Ozone Reaction Estimation

Fraction sorbed to airborne particulates (phi):
0.00017 (Junge-Pankow, Mackay avg)
0.000103 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 33.83 L/kg (MCI method)
Log Koc: 1.529 (MCI method)
Koc : 2.614 L/kg (Kow method)
Log Koc: 0.417 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -2.0127 days (HL = 0.009712 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.047 (BCF = 0.8973)
Log BAF Arnot-Gobas method (upper trophic) = -0.047 (BAF = 0.8973)
log Kow used: -0.84 (user entered)

Volatilization from Water:
Henry LC: 8.88E-010 atm-m3/mole (estimated by Group SAR Method)
Half-Life from Model River: 6.856E+005 hours (2.857E+004 days)
Half-Life from Model Lake : 7.48E+006 hours (3.117E+005 days)

Removal In Wastewater Treatment:
Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.76 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**0.00797**	**1.46**	**1000**
Water	**25.3**	**900**	**1000**
Soil	**74.6**	**1.8e+003**	**1000**
Sediment	**0.0889**	**8.1e+003**	**0**

Persistence Time: 1.29e+003 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.00797	1.46	1000
Water	25.3	900	1000
water	(25.3)		
biota	(1.83e-007)		

suspended sediment (0.00128)
Soil 74.6 1.8e+003 1000
Sediment 0.0889 8.1e+003 0
Persistence Time: 1.29e+003 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0113	1.46	1000
Water	47.1	900	1000
water	(47.1)		
biota	(3.4e-007)		
suspended sediment	(4.18e-006)		
Soil	52.8	1.8e+003	1000
Sediment	0.0904	8.1e+003	0

Persistence Time: 916 hr

APPENDIX G: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for PPD. This is a new assessment.

Table 5: Change in GreenScreen® Benchmark™ for PPD

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
March 18, 2024	BM-2	v. 1.4	New GreenScreen® assessment.
April 5, 2024	BM-2	v. 1.4	No change in benchmark score. The endpoint score for single dose neurotoxicity (Ns) was changed from *M* to *vH,* and for skin irritation was changed from *L* to *M,* based on Washington Department of Ecology's feedback.

Licensed GreenScreen® Profilers

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