N,N'-BIS(1,4-DIMETHYLPENTYL)-P-PHENYLENEDIAMINE (77PPD)

(CAS #3081-14-9)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 9, 2021

Expiration Date: November 9, 2026

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GreenScreen® Executive Summary for N,N'-Bis(1,4-dimethylpentyl)-p-phenylenediamine (77PPD) (CAS #3081-14-9)

N,N'-Bis(1,4-dimethylpentyl)-p-phenylenediamine (77PPD) is a member of the substituted p-phenylenediamines, which are used as antioxidants / antiozonants in rubber, fuel additives, or in monomer distillation. 77PPD is an oily, purple liquid, that is slightly less dense than water. Its log K_{ow} is 5.34; therefore, it has higher affinity for oil than water, and its overall low water solubility is higher at lower pH. Based on its high boiling point, and very low vapor pressure, it is not a volatile organic compound (VOC). 77PPD is not flammable or explosive.

GreenScreen® Summary Rating for 77PPD[1,2 3,4]: 77PPD 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 2a
  - Moderate Persistence-P + Moderate Bioaccumulation-B + Moderate Group I Human Toxicity (developmental toxicity-D)
  - Moderate P + Moderate B + Moderate Group II Human Toxicity (acute toxicity-AT and single dose systemic toxicity-STs)
  - Moderate P + Moderate B + Moderate Group II* Human Toxicity (respiratory sensitization-SnR*)
  - Moderate P + Moderate B + High Group II* Human Toxicity (skin sensitization-SnS*)
  - Moderate P + Moderate B + Very High Ecotoxicity (acute aquatic-AA and chronic aquatic-CA)
- Benchmark 2c
  - Moderate -P + Moderate Group I Human Toxicity (D)
  - Moderate P + Moderate Group II Human Toxicity (AT and STs)
  - Moderate P + Moderate Group II* Human Toxicity (SnR*)
  - Moderate P + High Group II* Human Toxicity (SnS*)
  - Moderate P + Very High Ecotoxicity (AA and CA)
- Benchmark 2e
  - Moderate Group I Human Toxicity (D)
- Benchmark 2f
  - High Group II* Human Toxicity (SnS*)
  - Very High Ecotoxicity (AA and CA)

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 77PPD meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if 77PPD were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

[1] 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.
[2] See Appendix A for a glossary of hazard endpoint acronyms.
[3] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[4] 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.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests to assess mutagenicity and genotoxicity, and QSAR modeling to assess endocrine activity, respiratory sensitization, persistence and bioaccumulation. 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 77PPD's NAMs dataset include application of *in vitro* UDS assay, lack of sufficient data for endocrine activity, respiratory sensitization, persistence, and bioaccumulation, and lack of validated methods for respiratory sensitization. 77PPD's Type II (extrapolation output) uncertainties include reliance on *in vitro* genotoxicity assays that examine apical events and capture only limited aspects of the complex metabolic processes that occur in mammalian systems, the uncertain *in vivo* relevance of *in silico* modeling of endocrine receptor binding activities, and the limitation of the ECHA framework for assessment of respiratory sensitization in consideration of non-immunological mechanisms, for which human data are the main data source. Some of 77PPD'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 77PPD

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*	*	*								
L	**L**	**L**	*M*	DG	**M**	**L**	**M**	*L*	DG	*H*	*M*	**L**	**L**	**vH**	**vH**	*H*	*M*	*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 N,N'-Bis(1,4-dimethylpentyl)-p-phenylenediamine (77PPD) (CAS #3081-14-9)

Method Version: GreenScreen® Version 1.4
Assessment Type[5]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Nancy Linde, M.S.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: October 15, 2021, November 8, 2021

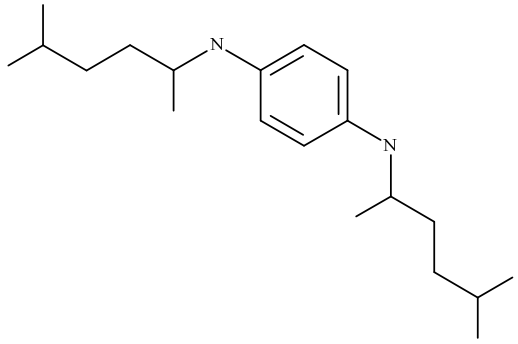
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: October 19, 2021, November 9, 2021

Expiration Date: November 9, 2026[6]

Chemical Name: N,N'-Bis(1,4-dimethylpentyl)-p-phenylenediamine (77PPD)

CAS Number: 3081-14-9

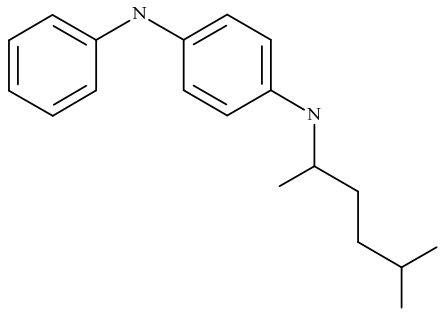
Chemical Structure(s):



Also called: 1 ,4-Benzenediamine, N,N'-bis(1,4-dimethylpentyl)-; N,N-Di(1,4-dimethylpentyl)-p-phenylenediamine; 1,4-Benzenediamine, N1,N4-bis(1,4-dimethylpentyl)-; p-Phenylenediamine, N,N'-bis(1,4-dimethylpentyl)-; EC 221-375-9 (ChemIDplus 2021)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
77PPD has a fairly robust dataset; however, ToxServices used 7PPD (N-(1,4-dimethylpentyl)-N'-phenylbenzene-1,4-diamine) (CAS #3081-01-4) as a surrogate for biodegradation. It differs from 77PPD by having one fewer 1,4-dimethylpentyl substituent on the aromatic amine.

[5] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[6] 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).



(CAS #3081-01-4) (ChemIDplus 2021)

Identify Applications/Functional Uses:
1. Antioxidant / antiozonant in rubber
2. Fuel additive
3. Monomer distillation
(U.S. EPA 2011)

Known Impurities[7]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for 77PPD[8,9 10,11]: 77PPD 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 2a
  - Moderate Persistence-P + Moderate Bioaccumulation-B + Moderate Group I Human Toxicity (developmental toxicity-D)
  - Moderate P + Moderate B + Moderate Group II Human Toxicity (acute toxicity-AT and single dose systemic toxicity-STs)
  - Moderate P + Moderate B + Moderate Group II* Human Toxicity (respiratory sensitization-SnR*)
  - Moderate P + Moderate B + High Group II* Human Toxicity (skin sensitization-SnS*)
  - Moderate P + Moderate B + Very High Ecotoxicity (acute aquatic-AA and chronic aquatic-CA)
- Benchmark 2c
  - Moderate -P + Moderate Group I Human Toxicity (D)
  - Moderate P + Moderate Group II Human Toxicity (AT and STs)
  - Moderate P + Moderate Group II* Human Toxicity (SnR*)
  - Moderate P + High Group II* Human Toxicity (SnS*)
  - Moderate P + Very High Ecotoxicity (AA and CA)
- Benchmark 2e

[7] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[8] 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.
[9] See Appendix A for a glossary of hazard endpoint acronyms.
[10] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[11] 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.

  - Moderate Group I Human Toxicity (D)
- Benchmark 2f
  - High Group II* Human Toxicity (SnS*)
  - Very High Ecotoxicity (AA and CA)

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 77PPD meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if 77PPD were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for 77PPD

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*	*	*								
L	**L**	**L**	*M*	DG	**M**	**L**	**M**	*L*	DG	*H*	*M*	**L**	**L**	**vH**	**vH**	*H*	*M*	*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.

Environmental Transformation Products

77PPD's half-life in water, due to hydrolysis, is estimated at 5.15 hours at pH 7. The primary hydrolysis product is expected to be N-1,4-dimethylpentyl-p-phenol, which rapidly hydrolyzes to N-phenyl-p-benzoquinone mono-imine. The latter compound is expected to be somewhat persistent in the environment (ECHA 2021a). As neither hydrolysis products are LT-1 chemicals, the benchmark score of 77PPD is not affected by the hazards of the hydrolysis products. No other environmental transformation products were identified.

Table 1: Environmental Transformation Product Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[12,13]
Environmental Release	Hydrolysis	N-1,4-Dimethylpentyl-p-phenol	N/A	Yes	No	N/A
Environmental Release	Hydrolysis	N-Phenyl-p-benzoquinone mono-imine	N/A	Yes	Yes	N/A

[12] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[13] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

Introduction

Although 77PPD is a high production volume (HPV) chemical, industrial processes were claimed confidential, and no commercial or consumer uses were identified (U.S. EPA 2011). Based on similarity to other phenylenediamines, it is presumed to be used as an antioxidant / antiozonant, fuel additive, and in monomer distillation.

ToxServices assessed 77PPD against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

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 2021a). 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).

77PPD is not currently 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 2021) 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),[14] 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 77PPD can be found in Appendix C.

- 77PPD is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- 77PPD is listed on the U.S. DOT list as a Hazard Class 6.1 chemical, Packing Group III (see Phenylenediamines (o-; m-; p-).
- 77PPD is on the following list for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - German FEA – Substances Hazardous to Waters – Class 3 – Severe Hazard to Waters

Hazard Statement and Occupational Control

No European Union (EU) harmonized Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for 77PPD, however notified hazard statements by the majority of notifiers and/or joint submissions were identified as indicated in Table 2. General personal protective equipment (PPE) recommendations are presented in Table 3, below. No occupational exposure limits (OELs) were identified.

Table 2: GHS H Statements for 77PPD (CAS #3081-14-9) (ECHA 2021b)

H Statement	H Statement Details
H302	Harmful if swallowed (Acute Tox. 4)
H317	May cause an allergic skin reaction (Skin Sens. 1)

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

Table 2: GHS H Statements for 77PPD (CAS #3081-14-9) (ECHA 2021b)	
H Statement	**H Statement Details**
H400	Very toxic to aquatic life (Aquatic Acute 1)
H410	Very toxic to aquatic life with long lasting effects (Aquatic Chronic 1)

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for 77PPD (CAS #3081-14-9)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
P280 (Wear protective gloves)	Eastman 2019	None	

Physicochemical Properties of 77PPD

77PPD is a dark red liquid that is non-volatile and slightly soluble in water. The partition coefficient of 5.34 indicates a bioaccumulation potential.

Table 4: Physical and Chemical Properties of 77PPD (CAS #3081-14-9)		
Property	**Value**	**Reference**
Molecular formula	C20H36N2	ChemIDplus 2021
SMILES Notation	CC(C)CCC(C)Nc1ccc(NC(C)CCC(C)C)cc1	ChemIDplus 2021
Molecular weight	304.52	U.S. EPA 2011
Physical state	Liquid	U.S. EPA 2011
Appearance	Dark red / magenta liquid; Oily, purple, slight, amine-like odor	ECHA 2021a; Eastman 2019
Melting point	-36°C (measured); <-50°C (EU Method A.1)	U.S. EPA 2011; ECHA 2021a
Boiling point	377°C at 760 mmHg (measured); >164 - < 169°C (method not specified)	U.S. EPA 2011; ECHA 2021a
Vapor pressure	<1.5E-6 hPa at 25°C (OECD 104)	ECHA 2021a
Water solubility	21 mg/L at pH 5 at 22°C (OECD 105), 0.8 mg/L at pH 9 at 22°C (OECD 105)	ECHA 2021a
Dissociation constant	7.5 at 20°C (OECD 112)	ECHA 2021a
Density/specific gravity	0.909 at 20 °C (DIN 51757 Verfahren D)	ECHA 2021a
Partition coefficient	Log K_{ow} = 5.34 (OECD 107)	ECHA 2021a

Toxicokinetics

No toxicokinetic data were found for 77PPD. Based on its low molecular weight of 304.5132 g/mol, and measured log K_{ow} of 5.34, it is expected to be bioavailable if ingested. It is also known to rapidly hydrolyze in water, and would be expected to rapidly hydrolyze in the body as well (ECHA 2021a). As it is moderately toxic following acute and repeated oral exposure, systemic absorption is presumed following oral exposure. As it is highly sensitizing to the skin, dermal absorption is also presumed either for 77PPD itself, or a metabolite.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
77PPD was assigned a score of Low for carcinogenicity based on negative results in a 2-year study in rats. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low based on limited study details reported in the public literature.

- 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 2021a
  - 77PPD was evaluated in a non-GLP-compliant chronic oral toxicity study (guideline not specified). Charles River CD Outbred albino rats were exposed to the test substance (purity not specified) in the diet for 2 years at 0, 30, 100, or 300 ppm, equivalent to 0, 2.25, 7.5, or 22.5 mg/kg/day (50/sex/dose) according to the ECHA record. Slight reductions in body weight (-8 to -13%) and body weight gain (-9 to -16%) were recorded in high dose animals throughout the study. There were no significant effects on mortality, clinical observations, food consumption, hematology, clinical chemistry, urinalyses, gross pathology, organ weights (absolute and relative), or histopathology. A severe respiratory infection affected all groups at 17 months, and all animals were treated with tetracycline hydrochloride for 2 weeks (Reliability 2, reliable with restrictions). Although not stated in the dossier, it is implied the test substance was not carcinogenic under the conditions of the study.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L
77PPD was assigned a score of Low for mutagenicity/genotoxicity based on *in vitro* data that were consistently negative for mutagenicity and clastogenicity in several assays, which meets the criteria for GHS not classified. 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 numerous studies with the target compound.

- 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 2021a (only studies with reliability scores of 1 (reliable without restriction) and 2 (reliable with restrictions) are included in this report)
  - 77PPD was evaluated in a GLP-compliant bacterial reverse mutation assay performed according to OECD 471. *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 were exposed to the test substance (as Santoflex 77, 100% purity) at up to 10 µg/plate without activation, and up to 200 µg/plate with activation. Results were negative for increased mutations in all strains, at all concentrations, with and without activation. Controls performed as expected. The highest concentrations were based on cytotoxicity. Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 1, reliable without restriction).
  - 77PPD was evaluated in a non-GLP-compliant reverse mutation assay in bacteria and yeast (guideline not specified). *S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538, and *Saccharomyces cerevisiae* strain D4, were exposed to the test substance (as Santoflex

77, purity not specified) at up to 5 µL/plate with and without activation. Results were negative for increased mutations in all strains of bacteria and yeast, at all concentrations, with and without activation. Controls performed as expected. The highest concentrations were based on cytotoxicity. Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 2, reliable with restrictions).

- 77PPD was evaluated in a non-GLP-compliant reverse mutation assay in bacteria and yeast (guideline not specified). *S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538, and *S. cerevisiae* strain D4, were exposed to the test substance (as Santoflex 77, purity not specified) at up to 5 µL/plate without activation, and up to 10 µL/plate with activation. Results were negative for increased mutations in all strains of bacteria and yeast, at all concentrations, with and without activation. Controls performed as expected. The highest concentrations were based on cytotoxicity. Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 2, reliable with restrictions).
- 77PPD was evaluated in a non-GLP-compliant reverse mutation assay in bacteria (guideline not specified). *S. typhimurium* TA98 and TA100 were exposed to the test substance (purity not specified) at up to 5 mg/plate without activation, and up to 10 µL/plate with activation. Results were negative for increased mutations in both strains, with and without activation (no further details provided). Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 2, reliable with restrictions).
- 77PPD was evaluated in a bacterial reverse mutation assay performed according to NTP standard protocol (GLP not specified). *S. typhimurium* TA98, TA100, TA1535, and TA1537 were exposed to the test substance (purity not specified) at up to 33 µg/plate without activation, and up to 333 µg/plate with activation. Results were negative for increased mutations in both strains, with and without activation (no further details provided). Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 2, reliable with restrictions).
- 77PPD was evaluated in a GLP-compliant *in vitro* mammalian cell gene mutation assay performed according to OECD 476. Chinese hamster ovary (CHO) cells were exposed to the test substance (as Santoflex 77, 100% purity), at up to 7.5 µg/mL without activation, and up to 30 µg/mL with activation. Results were negative for increased mutations at the hgprt locus at all concentrations, with and without activation. Controls performed as expected. The highest concentrations were based on cytotoxicity. Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 1, reliable without restriction).
- 77PPD was evaluated in an *in vitro* chromosome aberration assay performed according to OECD 473 (GLP not specified). CHO cells were exposed to the test substance (purity not specified), at up to 16 µg/mL with and without activation. The harvest time without activation was 12 hours. Activated cells were treated for 2 hours, and were harvested at 13 hours. Results were negative for increased chromosomal aberrations compared to controls at all concentrations, with and without activation. Controls performed as expected. Authors concluded the test substance was negative for chromosomal aberrations under the conditions of the test (Reliability 2, reliable with restrictions).
- 77PPD was evaluated in a non-GLP-compliant *in vitro* sister chromatid exchange (SCE) assay to performed to NTP standard protocol. CHO cells were exposed to the test substance (purity not specified), at up to 5 µg/mL without activation and 16 µg/mL with activation in Experiment 1, and up to 7.5 µg/mL without activation and 5 µg/mL with activation in Experiment 2. Results were negative for increases in sister chromatid exchanges in the CHO cells at all concentrations, with and without activation. Controls performed as expected.

Authors concluded the test substance was negative for sister chromatid exchanges under the conditions of the test (Reliability 2, reliable with restrictions).

- 77PPD was evaluated in a GLP-compliant *in vitro* unscheduled DNA synthesis (UDS) assay (guideline not specified). Rat primary hepatocytes were exposed to the test substance (as Santoflex 77, 100% purity), at up to 1,000 µg/mL in experiment 1, and up to 20 µg/mL in experiment 2. Results were negative for increased UDS at all concentrations. Controls performed as expected. Authors concluded the test substance was negative for UDS under the conditions of the test (Reliability 2, reliable with restrictions).

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

77PPD was assigned a score of Low for reproductive toxicity based on lack of indications of reproductive toxicity in rats in a GLP-compliant 3-generation study. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high based on multi-generational data for the target compound.

- 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 2021a
  - 77PPD was evaluated in a non-GLP-compliant 3-generation reproductive toxicity study performed in 1981 (guideline not specified). Charles River CD albino rats (8 males and 16 females per group) were exposed to the test substance (as Santoflex 77, purity not specified) in the feed with acetone as the vehicle at 0, 30, 100, or 300 ppm (equivalent to approximately 0, 2.25, 7.5, and 22.5 mg/kg/day, respectively). Males and females at 300 ppm had slight but statistically significant reduced body weight gains compared to controls in F0, F1, and F2 animals. Food consumption was measured in F0 animals, and was significantly reduced in week 9 at 300 ppm (statistical significance not reported), which authors speculated was due to poor palatability and noted the animals in this group continuously kicked the food out. Kidney weights were reduced in F0, F1, and F2 generations at 300 ppm compared to controls. Liver weights were reduced in F1 and F2 animals at 300 ppm compared to controls. Mortality was high in all parental animals throughout the study, but there was no apparent dose-relationship, and post-mortem pathology results were similar in all groups with lung lesions suggestive of respiratory infection. There were no significant findings based on clinical observations, histopathology, reproductive parameters (mating indices, fertility indices, and incidence of parturition). The number of pups surviving to weaning was reduced at the highest dose in F1b, F2a, F2b, F3a, and F3b litters, and the number surviving at the mid-dose was reduced in F2a, F3a, and F3b litters. Body weights of weanlings at 300 ppm were significantly reduced for F1b males, and F2 and F3 males and females, and slightly reduced for mid-dose litters. Authors reported a NOAEL for reproductive toxicity at 300 ppm, the highest concentration tested. Authors reported a NOAEL for parental systemic toxicity at 100 ppm, and LOAEL of 300 ppm, based on body weight and weight gain reduction, and reduced liver and kidney weights (Reliability 2, reliable with restrictions).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*

77PPD was assigned a score of Moderate for developmental toxicity based on reduced pup body weights and survival to weaning in a 3-generation oral study in rats at a dose causing maternal systemic toxicity. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity

when there is limited or marginal evidence in animals (CPA 2018b). The confidence in the score is low as it is unclear if the observed developmental effects were secondary to maternal systemic toxicity.

- 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 2021a (note due to the large volume of available reliable data, additional study summaries for range-finding studies, which include lower numbers of animals, are not included in the weight of evidence, and are not summarized here).
    - 77PPD was evaluated in a GLP-compliant prenatal developmental toxicity study performed according to OECD 414. Charles River CD rats were exposed to the test substance (as Santoflex 77, 100% purity) by gavage in corn oil on gestation days (GD) 6 to 15, at 0, 25, 75, or 150 mg/kg/day (25/sex/group). The study was terminated on GD 20. Mortality was increased with 4 deaths in dams at 150 mg/kg/day between GD 16-17, and 1 dam at 75 mg/kg/day on GD 17. Body weight loss was measured at 150 mg/kg/day on GD 6-9, and body weight gain was reduced for the overall study period at 75 and 150 mg/kg/day. There were no significant findings at Cesarean section based on number of pregnant dams, fetus viability, total number of implantations, number of corpora lutea per dam, pre- or post-implantation loss, or sex ratios. There was a significant increase in fetal body weight at the low dose group, but it was considered not toxicologically significant. There were no significant differences on skeletal or visceral examinations. Authors assigned the NOAEL for developmental toxicity at 150 mg/kg/day, the highest dose tested. Authors assigned the NOAEL for maternal systemic toxicity at 25 mg/kg/day, and LOAEL at 75 mg/kg/day (critical effect not specified) (Reliability 1, reliable without restriction). *ToxServices assumed the critical effects for parental systemic toxicity was decreased body weights and increased mortality in dams at ≥ 75 mg/kg/day.*
    - 77PPD was evaluated in a non-GLP-compliant, non-guideline teratogenicity study in rabbits. New Zealand White rabbits (10-11 per group) were artificially inseminated, and then were exposed to the test substance (as Santoflex 77, purity not specified) in gelatin capsules administered orally at 0, 3, or 10 mg/kg/day on GD 6 to 18. The study was terminated on GD 29. Mortality was high in all groups during the study with 5/17 deaths in controls, 3/17 at 3 mg/kg/day, and 7/21 at 10 mg/kg/day. Of these deaths, all those of the control and mid-dose groups, and 4/7 at 10 mg/kg/day were due to respiratory insufficiency or failure. Three high dose animals aborted and were found dead during the study, and gross pathology identified ulcerated mucosa of the stomach. There were no significant findings based on clinical observations or body weights. For reproductive parameters, there were no significant findings based on number of implantation sites, resorptions, or ratio of live young. One high dose fetus had bilateral talipomanus, and while historical data were not available, authors noted it is not uncommon in control animals in this laboratory, and therefore the single incidence was not considered a teratogenic effect that could be attributed to prenatal exposure to the test substance. There were no significant differences in offspring body weights. The 24-hour viability index of pups from both treatment groups was significantly reduced compared to controls (93.8%, 76.6%, and 76.0%, respectively). There were no abnormal findings based on necropsy of the pups at study termination based on visceral examinations, skeletal abnormalities, or skeletal malformations. NOAELs and LOAELs were not reported (Reliability 2, reliable with restrictions including limited documented study report, which meets basic scientific principles, but with methodological limitation (e.g. only two concentration evaluated, low number of pregnant rabbits evaluated, no individual data available for mortality, reproductive effects, gross fetal abnormalities

offspring body weights, clinical signs, fetal malformations; no raw data available, no historical control data available); in addition all non-pregnant does died because of respiratory insufficiency or failure; in other studies from this laboratory (same year) the occurrence of respiratory diseases were recorded, which caused high mortality rates.). *ToxServices notes based on the number of study and reporting limitations, this study is not sufficient for an assessment and is not convincing for expert judgement, therefore it meets the criteria for Klimisch 3, not reliable. Accordingly, this study is not included in the weight-of-evidence.*

- As summarized above, 77PPD was evaluated in a non-GLP-compliant 3-generation reproductive toxicity study performed in 1981 (guideline not specified). Charles River CD albino rats (8 males and 16 females per group) were exposed to the test substance (as Santoflex 77, purity not specified) in the feed with acetone as the vehicle at 0, 30, 100, or 300 ppm (equivalent to approximately 0, 2.25, 7.5, and 22.5 mg/kg/day, respectively). Males and females at 300 ppm had slight but statistically significant reduced body weight gains compared to controls in F0, F1, and F2 animals. Food consumption was measured in F0 animals, and was significantly reduced in week 9 at 300 ppm (statistical significance not reported), which authors speculated was due to poor palatability and noted the animals in this group continuously kicked the food out. Kidney weights were reduced in F0, F1, and F2 generations at 300 ppm compared to controls. Liver weights were reduced in F1 and F2 animals at 300 ppm compared to controls. Mortality was high in all parental animals throughout the study, but there was no apparent dose-relationship, and post-mortem pathology results were similar in all groups with lung lesions suggestive of respiratory infection. There were no significant findings based on clinical observations, histopathology, reproductive parameters (mating indices, fertility indices, and incidence of parturition). The number of pups surviving to weaning was reduced at the highest dose in F1b, F2a, F2b, F3a, and F3b litters, and the number surviving at the mid-dose was reduced in F2a, F3a, and F3b litters. Body weights of weanlings at 300 ppm were significantly reduced for F1b males, and F2 and F3 males and females, and slightly reduced for mid-dose litters. Authors reported a NOAEL for reproductive toxicity at 300 ppm, the highest concentration tested. Authors reported a NOAEL for parental systemic toxicity at 100 ppm, and LOAEL of 300 ppm, based on body weight and weight gain reduction, and reduced liver and kidney weights (Reliability 2, reliable with restrictions). *While pups body weights and survival to weaning were reduced at the highest concentration in all three generations, it is unclear if these effects were secondary to parental systemic toxicity, and a developmental NOAEL and LOAEL cannot be assigned.*

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

77PPD was assigned a score of Data Gap for endocrine activity based on insufficient data. While the weight of evidence from modeling suggests low concerns for endocrine activity, the reliability of the predictions is not known, and no measured data *in vivo* were found.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2021b
  - 77PPD has not been evaluated for endocrine activity as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century.
- DTU 2021
  - Modeling predictions that were within the applicability domain are as follows (Appendix D):

- 77PPD was predicted to be negative for estrogen receptor α binding with the Full training set (Human *in vitro*) using the CASE Ultra method, and positive using the SciQSAR method.
- 77PPD was predicted to be negative for estrogen receptor β binding with the Full training set (Human *in vitro*) using the model battery consisting of in domain and negative predictions by the CASE Ultra, Leadscope, and SciQSAR models.
- 77PPD was predicted to be negative for estrogen receptor α activation (Human *in vitro*) using the model battery consisting of in domain and negative predictions by the Leadscope, and SciQSAR models.
- 77PPD was predicted to be negative for estrogen receptor activation, CERAPP data (*in vitro*) using the Leadscope method.
- 77PPD was predicted to be negative for androgen receptor inhibition (Human *in vitro*) using the model battery consisting of negative and in domain predictions by CASE Ultra, Leadscope, and SciQSAR models.
- 77PPD was predicted to be negative for androgen receptor activation, CoMPARA data (*in vitro*) using the Leadscope method.

Group II and II* Human Health Effects (Group II and II* Human)

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): M

77PPD was assigned a score of Moderate for acute toxicity based on the lowest reported reliable oral LD_{50} at 730 mg/kg in rats, and the lowest reported reliable dermal LD_{50} of >3,160 mg/kg in rabbits. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when the oral LD_{50} is in the range of >300 and ≤ 2,000 mg/kg (CPA 2018b). The confidence in the score is high based on reliable data for the target compound.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - DK-EPA – Danish Advisory List – Acute Tox. 4 – Harmful if swallowed (modeled)
- ECHA 2021a (Only studies assigned reliability scores of 1 (reliable without restriction) and 2 (reliable with restrictions) are included below).
  - *Oral:* 77PPD was evaluated in an acute oral toxicity study (guideline and GLP not specified). Sprague-Dawley rats were exposed to the test substance by gavage (no vehicle) at 501, 631, 794, or 1,000 mg/kg (5 males and females combined per dose, no control animals). Authors calculated the LD_{50} at 730 mg/kg (Reliability 2, reliable with restrictions).
  - *Oral:* 77PPD was evaluated in an acute oral toxicity study (guideline and GLP not specified). Sprague-Dawley rats were exposed to the test substance as a 25% suspension in corn oil. The test substance was administered by gavage at 3,160, 3,980, 5,010, and 6,310 mg/kg (5 males and females combined per dose, no control animals). Authors calculated the LD_{50} at 4,500 mg/kg (Reliability 2, reliable with restrictions).
  - *Dermal:* 77PPD was evaluated in an acute dermal toxicity study (guideline not specified, pre-GLP). New Zealand White rabbits were exposed to the test substance under occlusion for 24 hours at 1,260, 2,000, 3,160, 5,010, or 7,940 mg/kg (1/sex/dose, no control animals).

There were no deaths at 3,160 mg/kg, and 100% deaths at ≥ 5,010 mg/kg. Authors assigned the LD_{50} at > 3,160 mg/kg (Reliability 2, reliable with restrictions).

- *Dermal:* 77PPD was evaluated in an acute dermal toxicity study (guideline not specified, pre-GLP). New Zealand White rabbits were exposed to the test substance as a 40% suspension in corn oil, under occlusion for 24 hours at 5,010, or 7,940 mg/kg (1 female at 5,010 mg/kg, and 1 male and 1 female at 7,940 mg/kg, no control animals). There were no deaths. Authors assigned the LD_{50} at > 7,940 mg/kg (Reliability 2, reliable with restrictions).

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

77PPD was assigned a score of Low for systemic toxicity (single dose) based on numerous acute oral and dermal toxicity studies in which there were no reported indications of systemic effects at sub-lethal doses. Additionally, 77PPD does not present an aspiration hazard. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality studies for the target substance.

- 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 2021a
  - As 77PPD is not a hydrocarbon, chlorinated hydrocarbon, primary alcohol, or ketone, it does not meet the criteria for GHS Category 1 classification.
  - The dynamic viscosity of 77PPD was measured at 28.6 mPa-s at 37.8°C (GLP-compliant, DIN 53015) (Reliability 1, reliable without restriction). *Kinematic viscosity = dynamic viscosity / density, therefore the kinematic viscosity of 77PPD is 28.6 mPa-s / 0.909 g/cm^3 = 31.46 mm^2/s, which exceeds the guidance value of 14 mm^2/s for GHS Category 2 classification.*
- Eastman 2019
  - The dynamic viscosity at 37.8 °C is 28.6 mPa-s, and the kinematic viscosity at 25°C is 56-85 mm^2/s (no further details provided).
- ECHA 2021a (Only studies assigned reliability scores of 1 (reliable without restriction) and 2 (reliable with restrictions) are included below).
  - *Oral:* 77PPD was evaluated in an acute oral toxicity study (guideline and GLP not specified). Sprague-Dawley rats were exposed to the test substance by gavage (no vehicle) at 501, 631, 794, or 1,000 mg/kg (5 males and females combined per dose, no control animals). Signs of intoxication included reduced appetite and activity at 4-6 days post-exposure in surviving animals, increasing weakness, collapse, and death. Gross autopsy of decedents identified hemorrhagic areas of the lungs, liver discoloration, and acute gastrointestinal inflammation (doses not specified). Viscera in surviving animals appeared normal at 10 days post-exposure. Authors calculated the LD_{50} at 730 mg/kg (Reliability 2, reliable with restrictions).
  - *Oral:* 77PPD was evaluated in an acute oral toxicity study (guideline and GLP not specified). Sprague-Dawley rats were exposed to the test substance as a 25% suspension in corn oil. The test substance was administered by gavage at 3,160, 3,980, 5,010, and 6,310 mg/kg (5 males and females combined per dose, no control animals). Signs of intoxication included reduced appetite and activity at 2-3 days post-exposure in surviving animals, increasing weakness, collapse, and death. Gross autopsy of decedents identified

hemorrhagic areas of the lungs and liver, and acute gastrointestinal inflammation (doses not specified). Viscera in surviving animals appeared normal at 7 days post-exposure. Authors calculated the LD_{50} at 4,500 mg/kg (Reliability 2, reliable with restrictions).

- *Dermal: 77PPD* was evaluated in an acute dermal toxicity study (guideline not specified, pre-GLP). New Zealand White rabbits were exposed to the test substance under occlusion for 24 hours at 1,260, 2,000, 3,160, 5,010, or 7,940 mg/kg (1/sex/dose, no control animals). There were no deaths at 3,160 mg/kg, and 100% deaths at ≥ 5,010 mg/kg. Clinical signs included reduced appetite and activity in survivors, increased weakness, collapse, and death 2 to 3 days after application. Observations at necropsy included lung hyperemia, liver discoloration, enlarged gall bladder, and gastrointestinal inflammation. Viscera appeared normal in 1 survivor at day 14, whereas 2 survivors had slight discoloration of the liver and kidneys. Authors assigned the LD_{50} at > 3,160 mg/kg (Reliability 2, reliable with restrictions).
- *Dermal:* 77PPD was evaluated in an acute dermal toxicity study (guideline not specified, pre-GLP). New Zealand White rabbits were exposed to the test substance as a 40% suspension in corn oil, under occlusion for 24 hours at 5,010, or 7,940 mg/kg (1 female at 5,010 mg/kg, and 1 male and 1 female at 7,940 mg/kg, no control animals). There were no deaths. Clinical signs included reduced appetite and activity 2 to 4 days after application. Viscera appeared normal at necropsy in all survivors at day 14. Authors assigned the LD_{50} at > 7,940 mg/kg (Reliability 2, reliable with restrictions).

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

77PPD was assigned a score of Moderate for systemic toxicity (repeated dose) based on two oral studies that provide a 90-day LOAEL of 22.82 mg/kg/day, and a 28-day LOAEL of 93.1 mg/kg/day. These values meet the criteria for GHS Category 2 classification. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when data meet GHS Category 2 classification (CPA 2018b). The confidence in the score is high based on high quality data for the target compound. It may be noted that no data were found for repeated dermal exposure, and one study for repeated inhalation exposure was considered unreliable.

- 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 2021a; U.S. EPA 2011
  - *Oral:* 77PPD was evaluated in a GLP-compliant subchronic toxicity study performed according to OECD 408. Sprague-Dawley rats were exposed to the test substance (100% purity) in the diet for 92-93 days at 0, 100, 250, or 500 ppm (males), and 0, 250, 500, or 750 ppm (females) (10/sex/dose). There were no significant findings based on mortality, clinical observations, food consumption, ophthalmology, hematology, gross examinations, or histopathology. Males at 250 and 500 ppm had slight body weight reduction, and reduced body weight gain (-5% and -9%, respectively) at study termination, but the difference was only statistically significant ($p < 0.01$) at 500 ppm. Females at ⩾250 ppm had slight body weight reduction, and reduced body weight gain (-11% and -23%, respectively) at study termination, and this effect was statistically significant at all three doses. Some clinical chemistry parameters were statistically significantly increased or decreased at 1.5 months and/or study termination, such as decreased mean alkaline phosphatase levels, increased mean serum glutamic oxaloacetic transaminase, and decreased mean serum glutamic pyruvic transaminase; however, there were no corresponding histopathological findings. There were

some effects on relative organ weights but they corresponded with decreased body weights and were considered secondary effects. Authors assigned a NOEL and LOAEL of 100 and 250 ppm, respectively, in males, based on decreased body weight, and reduced body weight gain. In females, the LOAEL was 250 ppm, the lowest dose tested, based on body weight reduction (-11% at study termination), and decreased body weight gain (-23% at study termination) (Reliability 1, reliable without restriction). U.S. EPA (2011) reports the NOEL of 100 ppm is equivalent to ~ 9.13 mg/kg/day, and the LOAEL of 250 ppm is equivalent to ~22.82 mg/kg/day. *A LOAEL of 22.82 mg/kg/day is in the range of GHS Category 2 at >10 and ⩽ 100 mg/kg/day.*

- *Oral:* 77PPD was evaluated in a GLP-compliant subacute oral toxicity study (guideline not specified). Sprague-Dawley rats were exposed to the test substance (100% active with 95.6% purity) in the diet for 28 days at 0, 100, 300, 500, 1,000, or 2,000 ppm (equivalent to 0, 8.0, 24.4, 37.7, 73.0, and 142.7 mg/kg/day for males, and 0, 9.3, 265.1, 43.3, 79.2, and 153.8 mg/kg/day for females) (5/sex/dose). There were no significant findings based on mortality, clinical observations, food consumption, hematology, gross examinations, or histopathology. Males had decreased body weight gain at ≥ 500 ppm, and in females at 2,000 ppm. Males and females had increased mean platelet counts at ≥ 1,000 ppm, and males had increased mean erythrocyte counts at ≥ 1,000 ppm. Numerous clinical chemistry parameters indicated treatment-related effects but there were no corresponding histopathological findings. Effects included reduced serum glutamic pyruvic transaminase in males and females at ≥500 ppm, slightly reduced fasting glucose in males at 2,000 ppm, slightly increased inorganic phosphorus in males at ≥1,000 ppm, increased alkaline phosphatase in females at 2,000 ppm, increased blood urea nitrogen in females at 2,000 ppm, and decreased total protein in females at 2,000 ppm. Mean terminal body weights were decreased in females at ≥1,000 and in males at ≥ 500 ppm. Differences in relative organ weights corresponded with decreased body weights and were considered secondary effects. Authors assigned a NOEL in females at 300 ppm, a NOAEL in males at 300 ppm, and a LOAEL in both sexes at 500 ppm based on decreased body weight and body weight gain, and decreases in serum glutamic pyruvic transaminase (Reliability 1, reliable without restriction). U.S. EPA (2011) reports the NOEL/NOAEL of 300 ppm is equivalent to 45.65 mg/kg/day, and the LOAEL of 500 ppm is equivalent to 91.30 mg/kg/day. *The GHS guidance values for Category 2, adjusted for a 28-day study, are >32 mg/kg/day and ≤ 320 (>10 mg/kg/day * 90 days/ 28 days, and ≤ 100 mg/kg/day * 90 days/ 28 days). Therefore, the LOAEL of 91.30 mg/kg/day meets the criteria for GHS Category 2.*
- *Oral:* As summarized above, 77PPD was evaluated in a non-GLP-compliant chronic oral toxicity study (guideline not specified). Charles River CD Outbred albino rats were exposed to the test substance (purity not specified) in the diet for 2 years at 0, 30, 100, or 300 ppm, equivalent to 0, 2.25, 7.5, or 22.5 mg/kg/day (50/sex/dose). Slight reductions in body weight (-8 to -13%) and body weight gain (-9 to -16%) were recorded in high dose animals throughout the study. There were no significant effects on mortality, clinical observations, food consumption, hematology, clinical chemistry, urinalyses, gross pathology, organ weights (absolute and relative), or histopathology. A severe respiratory infection affected all groups at 17 months, and all animals were treated with tetracycline hydrochloride for 2 weeks. Authors concluded a NOAEL of 100 ppm, and a LOAEL of 300 ppm based on slight decreases in body weight and body weight gain (Reliability 2, reliable with restrictions).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
77PPD was assigned a score of Low for neurotoxicity (single dose) based on lack of indications of neurotoxicity at sub-lethal doses in numerous acute exposure studies. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is reduced as specific neurotoxicity assessment were not carried out.

- 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 2021a
  - *Oral:* 77PPD was evaluated in an acute oral toxicity study (guideline and GLP not specified). Sprague-Dawley rats were exposed to the test substance by gavage (no vehicle) at 501, 631, 794, or 1,000 mg/kg (5 males and females combined per dose, no control animals). Signs of intoxication included reduced appetite and activity at 4-6 days post-exposure in surviving animals, increasing weakness, collapse, and death. Gross autopsy of decedents identified hemorrhagic areas of the lungs, liver discoloration, and acute gastrointestinal inflammation (doses not specified). Viscera in surviving animals appeared normal at 10 days post-exposure. Authors calculated the LD_{50} at 730 mg/kg (Reliability 2, reliable with restrictions).
  - *Oral:* 77PPD was evaluated in an acute oral toxicity study (guideline and GLP not specified). Sprague-Dawley rats were exposed to the test substance as a 25% suspension in corn oil. The test substance was administered by gavage at 3,160, 3,980, 5,010, and 6,310 mg/kg (5 males and females combined per dose, no control animals). Signs of intoxication included reduced appetite and activity at 2-3 days post-exposure in surviving animals, increasing weakness, collapse, and death. Gross autopsy of decedents identified hemorrhagic areas of the lungs and liver, and acute gastrointestinal inflammation (doses not specified). Viscera in surviving animals appeared normal at 7 days post-exposure. Authors calculated the LD_{50} at 4,500 mg/kg (Reliability 2, reliable with restrictions).
  - *Dermal: 77PPD* was evaluated in an acute dermal toxicity study (guideline not specified, pre-GLP). New Zealand White rabbits were exposed to the test substance under occlusion for 24 hours at 1,260, 2,000, 3,160, 5,010, or 7,940 mg/kg (1/sex/dose, no control animals). There were no deaths at 3,160 mg/kg, and 100% deaths at ≥ 5,010 mg/kg. Clinical signs included reduced appetite and activity in survivors, increased weakness, collapse, and death 2 to 3 days after application. Observations at necropsy included lung hyperemia, liver discoloration, enlarged gall bladder, and gastrointestinal inflammation. Viscera appeared normal in 1 survivor at day 14, whereas 2 survivors had slight discoloration of the liver and kidneys. Authors assigned the LD_{50} at > 3,160 mg/kg (Reliability 2, reliable with restrictions).
  - *Dermal:* 77PPD was evaluated in an acute dermal toxicity study (guideline not specified, pre-GLP). New Zealand White rabbits were exposed to the test substance as a 40% suspension in corn oil, under occlusion for 24 hours at 5,010, or 7,940 mg/kg (1 female at 5,010 mg/kg, and 1 male and 1 female at 7,940 mg/kg, no control animals). There were no deaths. Clinical signs included reduced appetite and activity 2 to 4 days after application. Viscera appeared normal at necropsy in all survivors at day 14. Authors assigned the LD_{50} at > 7,940 mg/kg (Reliability 2, reliable with restrictions).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
77PPD was assigned a score of Data Gap for neurotoxicity (repeated dose) based on lack of data. The above summarized repeated dose toxicity studies did not report performance of functional observational

batteries or assessments of motor activity. Accordingly, data are insufficient to rule out concerns for neurotoxicity following repeated exposure.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified for this endpoint.

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

77PPD was assigned a score of High for skin sensitization based on a 100% positive response rate in animals induced at 1% via intradermal exposure. This meets the criteria for GHS Category 1A (i.e., ≥60% responding at 1% intradermal induction), combined with positive predictions using QSAR modeling. GreenScreen® criteria classify chemicals as a High hazard for skin sensitization when adequate data exist and GHS classification is warranted (CPA 2018b). The confidence in the score is low as available studies are all of low reliability (Klimisch score of 4).

- 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 2021a
  - 77PPD was evaluated in a non-GLP-compliant guinea pig skin sensitization study (guideline not specified). Some slight sensitization was observed (no further details provided) (Reliability 4, not assignable).
  - 77PPD was evaluated in a non-GLP-compliant guinea pig maximization test performed according to the method of Magnusson and Kligman. Animals (15/dose) were induced by intradermal (1%) and epicutaneous (2%) administration in polyethylene glycol (PEG). Challenge was performed at 6.25% and 12.5% in PEG under occlusion. At 24 hours, 7/15 negative control animals challenged at 6.25% had positive reactions, and the mean reaction score was 0.5; by 48 hours, 4/15 animals had positive reactions with an average score of 0.3. At 24 hours, 14/15 negative control animals challenged at 12.5% had positive reactions, and the mean reaction score was 0.9; by 48 hours, 7/15 animals had positive reactions with an average score of 0.5. For animals treated by dermal induction, at 24 hours, 15/15 challenged at 6.25% had positive reactions, and the mean reaction score was 1.3; by 48 hours, 13/15 animals had positive reactions with an average score of 0.9. For animals treated by dermal induction, at 24 hours, 15/15 challenged at 12.5% had positive reactions, and the mean reaction score was 2.0; by 48 hours, 15/15 animals had positive reactions with an average score of 2.0. Authors of the ECHA dossier concluded the test substance was sensitizing based on higher mean scores in treated animals compared to negative controls. However, authors also state the test substance has an intense red color, therefore the reliability of the gradings in all groups is questionable (no further details provided) (Reliability 4, not assignable). *A positive response rate of 100% (i.e., 15/15 animals) at 1% induction meets the criteria for GHS Category 1A classification. It may also be noted that high quality skin irritation studies are summarized below, and there is no reported interference of test substance color.*
  - 77PPD was evaluated in a non-GLP-compliant guinea pig skin sensitization study (guideline not specified). Animals were induced twice by epicutaneous administration of a paste with 50% test substance. Challenge was performed at 10, 20, 30, 50 and 100% concentrations. Marked reddening of the skin was reported at the 100% dose level. Authors suggested a low or even no allergic potential of the test substance (no further details provided) (Reliability 4, not assignable).

- OECD 2021 (Appendix E)
    - 77PPD does not have any structural alerts for skin sensitization according to GHS or OASIS.
- Toxtree 2018 (Appendix F)
    - 77PPD has 1 structural alert for skin sensitization (i.e., Michael reaction acceptor or a precursor).
- VEGA 2021 (Appendix G)
    - 77PPD is predicted to be a skin sensitizer based on the CAESAR v. 2.1.6 model. The global applicability domain (AD) index value is 0.839, indicating high reliability.
    - 77PPD is predicted to be a skin sensitizer based on the IRFMN/JRC v. 1.0.0 model. The global AD index value is 0, indicating the prediction is not reliable.

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

77PPD was conservatively assigned a score of Moderate for respiratory sensitization based on extrapolation from skin sensitization data which correspond to GHS Category 1A, and presence of a structural alert for respiratory sensitization identified via QSAR modeling. GreenScreen® criteria classify chemicals as a High hazard for respiratory sensitization when data meet GHS Category 1 classification (CPA 2018b). The confidence in the score is low as the skin sensitization studies have low reliability, and no actual data were found for respiratory sensitization. Further, no data were available regarding the potency of the potential respiratory sensitization reactions to subclassify to Category 1A and 1B.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2021 (Appendix E)
    - 77PPD has a structural alert for respiratory sensitization, i.e., Pro-Michael Addition.
- No data were identified for the target compound for this endpoint. ECHA's guideline (ECHA 2017) states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). Therefore, as 77PPD tested positive for skin sensitization (see skin sensitization section above), and it has a structural alert for respiratory sensitization, it is reasonable to expect it may be a respiratory sensitizer and classified to GHS Category 1. No data were available to subclassify it as Category 1A and 1B.

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

77PPD was assigned a score of Low for skin irritation/corrosivity based on lack of skin irritation effects in two high quality studies. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data for the target compound.

- 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 2021a (Only studies with reliability scores of 1 (reliable without restriction) and 2 (reliable with restrictions) are included in this report below).
    - 77PPD was evaluated in a GLP-compliant acute dermal irritation study performed according to OECD 404. New Zealand White rabbits (n=3) were exposed to the test substance under semi-occlusive conditions (no vehicle) for 4 hours, followed by a 7-day observation period. There were no observations of erythema or edema in any of the animals at 24 or 48 hours, or 7 days post-exposure. Authors concluded the test substance was not irritating under the conditions of the test (Reliability 1, reliable without restriction).

- 77PPD was evaluated in a non-GLP-compliant acute dermal irritation study (guideline not specified). New Zealand White rabbits were exposed to the test substance on clipped or abraded skin (3 rabbits/group) under semi-occlusive conditions (no vehicle) for 4 hours, followed by a 10-day observation period. There were no irritating effects observed in any of the animals at 24 or 48 hours, or 10 days post-exposure, however there was a slight defatting effect based on skin flaking at 7 to 10 days. Authors concluded the test substance was not irritating under the conditions of the test (Reliability 1, reliable without restriction).

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): L
77PPD was assigned a score of Low for eye irritation/corrosivity based on data from two high quality studies from which the data exceed the GHS classification criteria. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data exist, and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data for the target substance.

- 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 2021a
  - 77PPD was evaluated in a GLP-compliant acute eye irritation study performed according to OECD 405. New Zealand White rabbits (n=3) were exposed to the test substance (93.9% purity) in the eye for 24 hours, followed by a 7-day observation period. All endpoints (cornea opacity, iris, conjunctiva, chemosis, discharge, and aqueous humor) had mean scores of 0 at 24, 48, and 72 hours, and 7 days post-exposure. Authors concluded the test substance was not irritating to the eye under the conditions of the test (Reliability 1, reliable without restriction).
  - 77PPD was evaluated in a non-GLP-compliant acute eye irritation study (guideline not specified). New Zealand White rabbits (n=6) were exposed to the test substance (96% purity) in the eye (undiluted) for 24 hours, followed by a 7-day observation period. The mean irritation index was 8.5 out of 110 based on observations of slight erythema, very slight to slight edema, and moderate to copious discharge at 24, 48, and 72 hours post-exposure, and all effects were fully reversed within 7 days. Authors concluded the test substance was not irritating to the eye under the conditions of the test (Reliability 2, reliable with restrictions).

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): vH
77PPD was assigned a score of Very High for acute aquatic toxicity based on multiple studies in fish, and one study in daphnia, that report LC_{50} values < 1 mg/L. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when the most sensitive trophic level has LC/EC_{50} values < 1 mg/L (CPA 2018b). The confidence in the score is high based on reliable data for the target compound.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - EC – CEPA DSL – Inherently Toxic in the Environment (iTE)

- ECHA, CAS 3081-14-9, 2021a (note due to the availability of reliable data on the target compound, the target compound studies with low reliability (reliability scores 3 or 4) and surrogate studies in the ECHA dossier are not included in the weight of evidence and are not summarized here).
    - 77PPD was evaluated in a 14-day toxicity study (guideline and GLP not specified) in *Pimephales promelas* (fathead minnows). Fish were exposed for 14 days under flow-through conditions at nominal concentrations of 0.03, 0.06, 0.12, 0.25, and 0.5 mg/L. The 96-hour LC_{50} was 0.06 mg/L (measured) and the 14-day LC_{50} was 0.05 mg/L (measured) (Reliability 2, reliable with restrictions).
    - 77PPD was evaluated in a 14-day toxicity study (GLP, OECD 204) in *P. promelas* (fathead minnows). Fish were exposed for 14 days under flow-through conditions at nominal concentrations of 0.04, 0.08, 015, 0.28, and 0.5 mg/L, and measured concentrations of 0.018, 0.046, 0.11, 0.22, and 0.45 mg/L. The 96-hour LC_{50} was 0.14 mg/L (measured) and the 14-day LC_{50} was 0.067 mg/L (measured) (Reliability 2, reliable with restrictions).
    - 77PPD was evaluated in a GLP-compliant acute toxicity study performed according to EPA-660/3-75-009. Midge larvae (*Paratanytarsus parthenogenetica*) were exposed to the test substance for 48 hours under static conditions. The 48-hour LC_{50} was 1.7 mg/L (nominal) (Reliability 2, reliable with restrictions).
    - 77PPD was evaluated in a GLP-compliant acute toxicity study performed according to EPA-660/3-75-009. *Daphnia magna* were exposed to the test substance for 48 hours under static conditions at up to 1.0 mg/L (nominal). The 48-hour LC_{50} was 0.37 mg/L (nominal) (Reliability 2, reliable with restrictions).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): vH
77PPD was assigned a score of Very High for chronic aquatic toxicity based on a 14-day LC_{50} of 0.05 mg/L, and a 14-day NOEC of 0.018 mg/L in fish. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when fish, invertebrates, or algae have chronic toxicity values ≤ 0.1 mg/L (CPA 2018b). The confidence in the score is high based on reliable data for the target compound.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - EC – CEPA DSL – Inherently Toxic in the Environment (iTE)
- ECHA 2021a
    - 77PPD was evaluated in a 14-day toxicity study (guideline and GLP not specified) in *P. promelas* (fathead minnows). Fish were exposed for 14 days under flow-through conditions at nominal concentrations of 0.03, 0.06, 0.12, 0.25, and 0.5 mg/L. The 14-day LC_{50} was 0.05 mg/L (measured) (Reliability 2, reliable with restrictions).
    - 77PPD was evaluated in a 14-day toxicity study (GLP, OECD 204) in *P. promelas* (fathead minnows). Fish were exposed for 14 days under flow-through conditions at nominal concentrations of 0.04, 0.08, 015, 0.28, and 0.5 mg/L, and measured concentrations of 0.018, 0.046, 0.11, 0.22, and 0.45 mg/L. The 14-day NOEC was 0.018 mg/L (measured) (Reliability 2, reliable with restrictions).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *H*
77PPD was assigned a score of High for persistence based on modeling which suggests soil will be the dominant medium, and the predicted half-life in soil is 75 days. The weight of evidence includes data

for the target compound demonstrating slow degradation in water, surrogate data demonstrating rapid primary degradation in soil, and rapid hydrolysis in water, with the generation of persistent degradation byproducts, and data demonstrating the degradation byproduct p-hydroquinone is highly toxic against bacteria. It may also be noted that the results on one ready biodegradation study (OECD 301B) suggest a half-life in water of 35 days, which corresponds with a GreenScreen® Moderate rating, but the score should be based on the degradation half-life in the dominant environmental compartment, which is predicted to be soil. GreenScreen® criteria classify chemicals as a High hazard for persistence when the dominant medium is soil, and the half-life is >60 and ≤ 180 days (CPA 2018b). The confidence in the score is low as it is based primarily on modeled data.

- 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 2021a
    - 77PPD was evaluated in a GLP-compliant Modified MITI test (OECD 301C). The test substance was exposed to domestic, non-adapted activated sludge under aerobic conditions at an initial concentration of 100 mg/L. Degradation was measured based on oxygen consumption. Degradation reached 12% in 28 days, and the reference substance, aniline, performed as expected. Authors concluded the test substance is not readily biodegradable (Reliability 2, reliable with restrictions).
    - 77PPD was evaluated in a non-GLP-compliant biodegradability test using the Monsanto shake flask procedure, similar to ASTM E35.24 and OECD 301B. The test substance was exposed to acclimated SCAS supernatant (starved) under aerobic conditions at an initial concentration of 25 mg/L. Degradation was measured based on CO_2 evolution. Degradation reached 50% in 35 days. Authors concluded the test substance is not inherently biodegradable (Reliability 2, reliable with restrictions).
    - *Surrogate 7PPD (N-(1,4-dimethylpentyl)-N'-phenylbenzene-1,4-diamine (CAS# 3081-01-4)*: 7PPD was evaluated for degradation in soil in a GLP-compliant test for aerobic and anaerobic transformation according to OECD 307. Persistence of the 14C-labelled test substance was evaluated in soil under aerobic conditions at 12°C in 4 samples for up to 56 days, each sample having different starting concentration and humidity values. DT50 values of the parent compound (indicative of primary degradation) ranged from 1.4 to 1.9 days in the 4 samples (Reliability 1, reliable without restriction).
    - *Surrogate 7PPD (N-(1,4-dimethylpentyl)-N'-phenylbenzene-1,4-diamine (CAS# 3081-01-4)*: In another OECD 307 test with surrogate 7PPD, rapid primary degradation was measured at 1.5 days, however the transformation byproducts, 7QDI (1-N-(5-methyl-hexan-2-yl)-4-N-phenylcyclohexa-2,5-dione-4,4-diimine) cis- and trans isomers had DT50 values of 57.9 to 79.7 days, and DT90 values of 192 to 265 days, suggesting the transformation products are persistent in the environment (Reliability 1, reliable without restriction).
    - Authors of the REACH dossier propose the slow biodegradation may be due to the fact that p-hydroquinone is highly toxic against bacteria, based on an EC_{50} of 71 mg/L, a NOEC of 1 mg/L, and the resulting PNEC(STP) is 0.71 mg/L.
    - The half-life of 77PPD in water, due to hydrolysis, is estimated at 5.15 hours at pH 7. The first hydrolysis byproduct is expected to be N-1,4-dimethylpentyl-p-phenol, which rapidly hydrolyzes to N-Phenyl-p-benzoquinone mono-imine. The latter compound is expected to somewhat persistent in the environment.
    - The photolysis screening test of 77PPD in water shows a half-life of 2 hours with radiation, and of 4 hours in the dark.
    - The calculated half-life for indirect hydrolysis in air is 3.7 hours.

- U.S. EPA 2017
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that 77PPD is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 65% will partition to soil with a half-life of 75 days, 22.9% will partition to sediment with a half-life of 337.5 days, and 12% will partition to water with a half-life of 37.5 days (Appendix H).

Bioaccumulation (B) Score (vH, H, M, L, or vL): *M*
77PPD was assigned a score of Moderate for bioaccumulation based on a modeled BAF of 614.6. GreenScreen® criteria classify chemicals as a Moderate hazard for bioaccumulation when the BAF is in the range of >500 and ≤1,000 (CPA 2018b). The confidence in the score is low as the measured K_{ow} is 5.34, which generally corresponds with a Very High hazard rating, however, measured data also demonstrate rapid hydrolysis in water with formation of compounds that have predicted BCF values in the range of Low to Very Low. Based on the weight of evidence, ToxServices assigned a Moderate hazard with low confidence.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - EC – CEPA DSL - Bioaccumulative
- ECHA 2021a
    - Authors of the REACH dossier suggest concerns for bioconcentration of 77PPD are low due to the rapid primary degradation of 77PPD in water (half-life 3.6 hours), and bioconcentration of the transformation products is also expected to be low. Specifically, 1,4-dimethylpentylamine is expected to have a low BCF based on a measured BCF of ≤ 17 for a similar compound, 1,3-dimethylbutylamine, in *Cyprinus carpio* (OECD 305C), and the calculated BCF for 1,4-dimethylpentylamino-p-phenol is 109 L/kg (BCFBAF v.3.01). Lastly, the transformation product 4-hydroxydiphenylamine has a measured BCF of 49 (OECD 305C). *Using the SMILES notation for 1,4-dimethylpentalamino-p-phenol (CC(C)CCC(C)Nc1ccccc1O) ToxServices modeled this hydrolysis byproduct and derived a log K_{ow} of 3.94, and BCF values of 185.5 and 99.98 using the regression-based and Arnot—Gobas models, respectively. Values >100 and ⩽500 correspond with a Low hazard rating, and those < 100 correspond with Very Low (CPA 2018b).*
- U.S. EPA 2017
    - Using the measured log K_{ow} value of 5.34, the BCFBAF v3.01 model predicts a BAF of 614.6 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix H).

<u>Physical Hazards (Physical)</u>

Reactivity (Rx) Score (vH, H, M, or L): *L*
77PPD was assigned a score of Low for reactivity based on lack of reactive functional groups in the chemical structure. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low based on the lack of measured data or authoritative listings.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of 77PPD. These procedures are listed in the GHS (UN 2021).

  - Based on the structure of its components or moieties, 77PPD is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix I).
  - Based on the structure of its components or moieties, 77PPD is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.
- Eastman 2019
  - Santoflex™ 77PD (100% CAS 3081-14-9) has an NFPA rating of 0 for instability (reactivity), the lowest hazard rating possible.

Flammability (F) Score (vH, H, M, or L): L

77PPD was assigned a score of Low for flammability based on a measured flash point of 178°C, which exceeds the criteria for GHS classification based on flash point > 93°C. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on measured data for the target compound.

- 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 2021a
  - The flash point of 77PPD was 178°C in a closed cup method (GLP-compliant, EU Method A.9) (Reliability 1, reliable without restriction).
- Eastman 2019
  - Santoflex™ 77PD (100% CAS 3081-14-9) has an NFPA and HMIS rating of 1 for flammability.

Use of New Approach Methodologies (NAMs)[15] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests to assess mutagenicity and genotoxicity, and QSAR modeling to assess endocrine activity, respiratory sensitization, persistence and bioaccumulation. NAMs are non-animal alternative 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 5, Type I (input data) uncertainties in 77PPD's NAMs dataset include application of *in vitro* UDS assay, lack of sufficient data for endocrine activity, respiratory sensitization, persistence, and bioaccumulation, and lack of validated methods for respiratory sensitization. 77PPD's Type II (extrapolation output) uncertainties include reliance on *in vitro* genotoxicity assays that examine apical events and capture only limited aspects of the complex metabolic processes that occur in mammalian systems, the uncertain *in vivo* relevance of *in silico* modeling of endocrine receptor binding activities, and the limitation of the ECHA framework for assessment of respiratory sensitization in consideration of non-immunological mechanisms, for which human data are the main data source. Some of 77PPD's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Genotoxicity:** The UDS assay method (OECD Guideline 482) has been deleted due to lack of use and poorer performance compared to other standard tests.[16] **Endocrine activity:** No measured *in vivo* data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Persistence:** Existing biodegradation data do not provide a half-life value for scorning **Bioaccumulation:** Log K_{ow} alone may overestimate bioaccumulation potential due to lack of consideration for biotransformation, and no experimental BCF/BAF values are available.

[15] 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).
[16] https://www.oecd.org/env/ehs/testing/Draft_Intro_Genotoxicity%20TGs%20September%202014.pdf

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[17]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[18] The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[19]. The *in vitro* UDS assay detects "longpatch repair" but is less sensitive for detection of "shortpatch repair". Mutagenic events may result from non-repair, misrepair, of misreplication of DNA lesions, and UDS gives no indication of fidelity of the repair process. It is possible that a mutagen interacts with DNA, but damage is not repaired by an excision repair process.[20] The *in vitro* SCE assay (as defined in OECD 479, a guideline deleted in 2014) detects reciprocal exchange of DNA without providing the underlying mechanism of action[21]. **Endocrine activity:** The *in vivo* relevance of *in silico* modeling of receptor binding activities is unknown due to lack of consideration of toxicokinetics. **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	

[17] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[18] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[19] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[20] https://www.oecd-ilibrary.org/environment/test-no-486-unscheduled-dna-synthesis-uds-test-with-mammalian-liver-cells-in-vivo_9789264071520-en#:~:text=The%20purpose%20of%20the%20unscheduled,physical%20agents%20in%20the%20liver.
[21] https://www.oecd.org/env/ehs/testing/Draft_Intro_Genotoxicity%20TGs%20September%202014.pdf

Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay / *in vitro* SCE assay / *in vitro* UDS assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: Danish QSAR
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	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™
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 77PPD (CAS #3081-14-9)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

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 / 77PPD / 3081-14-9	*L*	L	L	*M*	DG	M	L	M	*L*	DG	*H*	*M*	L	L	vH	vH	*H*	*M*	*L*	L

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
77PPD	2

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
77PPD	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 77PPD (CAS #3081-14-9)

3081-14-9
N,N'-Bis(1,4-dimethylpentyl)-p-phenylenediamine
ALSO CALLED 1,4-Benzenediamine, N,N'-bis(1,4-dimethylpentyl)-, 583049-46-1, 77PPD, Eastozone, Eastozone 33, Elas...
View all synonyms (12)

Share Profile

Hazards | Properties | Functional Uses | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

		Group I Human					Group II and II* Human								Ecotox			Fate		Physical		Mult	Non-GSLT			
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
All Hazards	LT-P1	-	-	-	-	-	pC	-	-	-	-	pC	-	pC	-	-	-	-	-	vH	-	-	pC	-	-	-	R

Hazard Lists

Download Lists

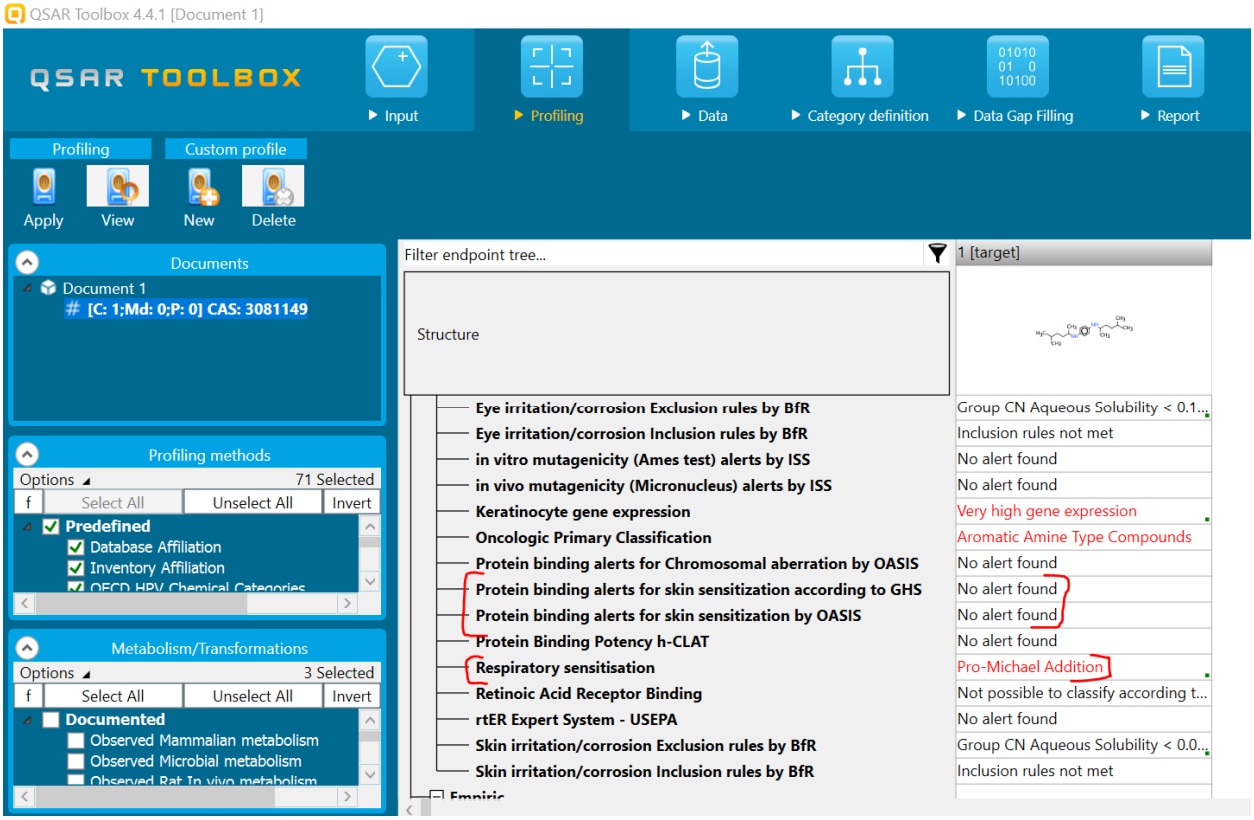
ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Acute Mammalian Toxicity	pC	NoGS	DK-EPA - Danish Advisory List	Acute Tox. 4 - Harmful if swallowed (modeled)	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H302 - Harmful if swallowed (unverified) [Acute toxicity (oral) - Category 4]	
Skin Sensitization	pC	NoGS	DK-EPA - Danish Advisory List	Skin Sens. 1 - May cause an allergic skin reaction (modeled)	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H317 - May cause an allergic skin reaction (unverified) [Skin sensitization - Category 1]	
Skin Irritation/Corrosivity	pC	NoGS	DK-EPA - Danish Advisory List	Skin Irrit. 2 - Causes skin irritation (modeled)	
Bioaccumulation	vH	LT-UNK	EC - CEPA DSL	Bioaccumulative	
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	
Acute aquatic toxicity; Chronic aquatic toxicity	U	LT-UNK	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	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]	

APPENDIX D: Danish QSAR Database Endocrine Activity Results for 77PPD (CAS #3018-14-9)

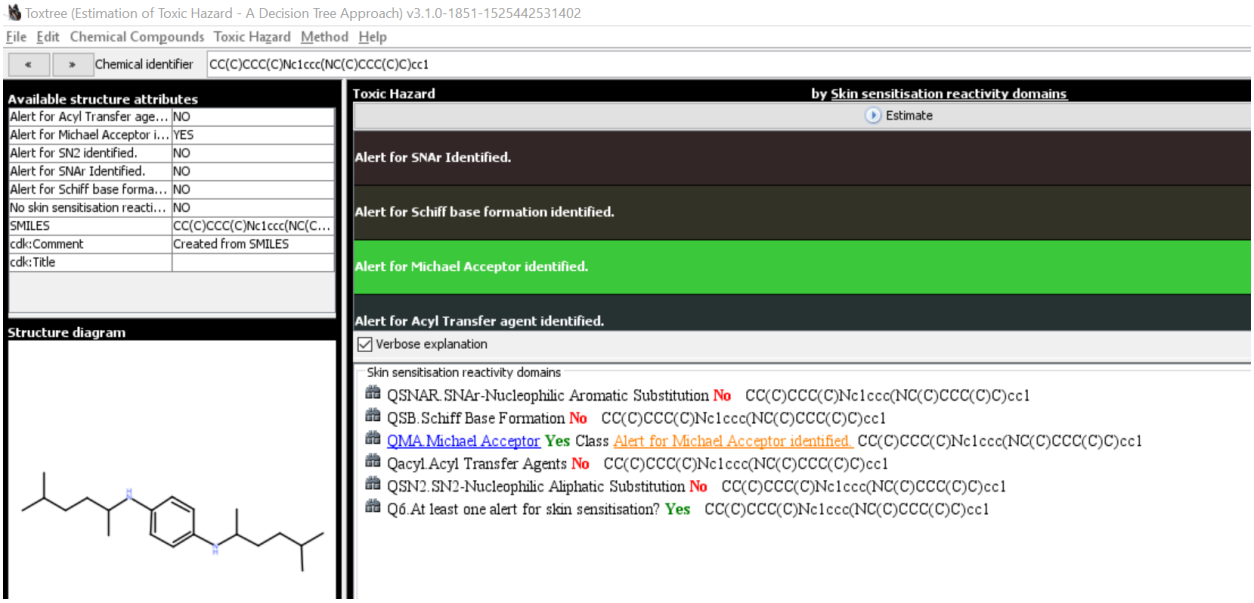
Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		INC_OUT	NEG_IN	INC_OUT	POS_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	INC_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_OUT	N/A

APPENDIX E: OECD Toolbox Profiling Results for 77PPD (CAS #3081-14-9)



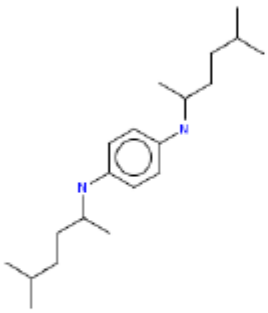
APPENDIX F: Toxtree Skin Sensitization Results for 77PPD (CAS #3081-14-9)



APPENDIX G: VEGA Skin Sensitization Results for 77PPD (CAS #3081-14-9)

1. Prediction Summary

Prediction for compound Molecule 0

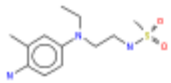


Prediction: Reliability:

Prediction is Sensitizer, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections. Anyway some issues could be not optimal:
- only moderately similar compounds with known experimental value in the training set have been found

Compound: Molecule 0
Compound SMILES: c1cc(ccc1NC(C)CCC(C)C)NC(C)CCC(C)C
Experimental value: -
Predicted skin sensitization activity: Sensitizer
O(Active): 0.54
O(Inactive): 0.47
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

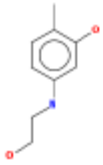
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 92 (Training set)
SMILES: O=S(=O)(NCCN(c1ccc(N)c(c1)C)CC)C
Similarity: 0.708

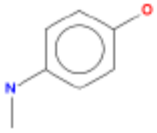
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #2

CAS: 55302-96-0
Dataset id: 149 (Training set)
SMILES: Oc1cc(ccc1C)NCCO
Similarity: 0.699

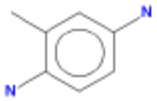
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #3

CAS: 150-75-4
Dataset id: 135 (Test set)
SMILES: Oc1ccc(cc1)NC
Similarity: 0.697

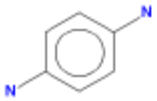
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #4

CAS: 95-70-5
Dataset id: 140 (Training set)
SMILES: Nc1ccc(N)c(c1)C
Similarity: 0.691

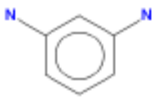
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #5

CAS: 106-50-3
Dataset id: 177 (Test set)
SMILES: Nc1ccc(N)cc1
Similarity: 0.685

Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #6

CAS: 108-45-2
Dataset id: 178 (Training set)
SMILES: Nc1cccc(N)c1
Similarity: 0.678

Experimental value: Sensitizer
Predicted value: Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.839
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.703
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

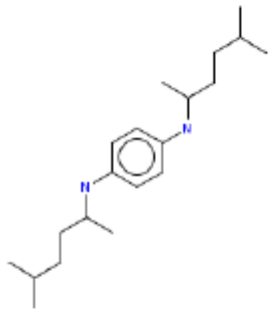
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound Molecule 0

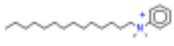


Prediction: Reliability:

Prediction is Sensitizer, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: c1cc(ccc1NC(C)CCC(C)C)NC(C)CCC(C)C
Experimental value: -
Predicted skin sensitization activity: Sensitizer
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

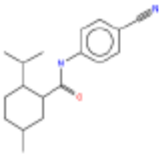
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 8001-54-5
Dataset id: 263 (Training set)
SMILES: c1ccc(cc1)[N+](C)(C)CCCCCCCCCCCCCC
Similarity: 0.855

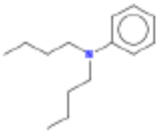
Experimental value: NON-Sensitizer
Predicted value: Sensitizer



Compound #2

CAS: 852379-28-3
Dataset id: 327 (Test set)
SMILES: N#Cc1ccc(cc1)NC(=O)C2CC(C)CCC2C(C)C
Similarity: 0.826

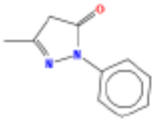
Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



Compound #3

CAS: 613-29-6
Dataset id: 166 (Training set)
SMILES: c1ccc(cc1)N(CCCC)CCCC
Similarity: 0.824

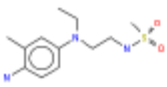
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #4

CAS: 89-25-8
Dataset id: 134 (Training set)
SMILES: O=C1N(N=C(C)C1)c2ccccc2
Similarity: 0.712

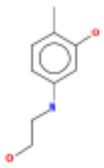
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #5

CAS: 25646-71-3
Dataset id: 135 (Training set)
SMILES: O=S(=O)(NCCN(c1ccc(N)c(c1)C)CC)C
Similarity: 0.708

Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #6

CAS: 55302-96-0
Dataset id: 121 (Training set)
SMILES: Oc1cc(ccc1C)NCCO
Similarity: 0.699

Experimental value: Sensitizer
Predicted value: Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.84 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.49 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.

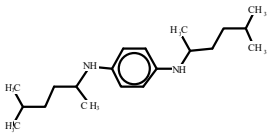
⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

APPENDIX H: EPI Suite™ Modeling Results for 77PPD (CAS #3081-14-9)

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

EPI Suite Results For CAS 3081-14-9



```
SMILES : N(c(ccc(NC(CCC(C)C)C)c1)c1)C(CCC(C)C)C
CHEM   : 1,4-Benzenediamine, N,N -bis(1,4-dimethylpentyl)-
MOL FOR: C20 H36 N2
MOL WT : 304.52
------------------------------ EPI SUMMARY (v4.11) --------------------------
Physical Property Inputs:
Log Kow (octanol-water):   5.34
Boiling Point (deg C)  :   377.00
Melting Point (deg C)  :   -36.00
Vapor Pressure (mm Hg) :   ------
Water Solubility (mg/L):   ------
Henry LC (atm-m3/mole) :   ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) =  6.30

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C):  364.35  (Adapted Stein & Brown method)
Melting Pt (deg C):  112.67  (Mean or Weighted MP)
VP(mm Hg,25 deg C):  2.99E-005  (Modified Grain method)
VP (Pa, 25 deg C) :  0.00399  (Modified Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L):  1.242
log Kow used: 5.34 (user entered)
melt pt used: -36.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) =  0.074747 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method :   9.72E-008  atm-m3/mole  (9.85E-003 Pa-m3/mole)
Group Method:   Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC:  not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC:  9.646E-006 atm-m3/mole  (9.774E-001 Pa-m3/mole)
VP:   2.99E-005 mm Hg (source: MPBPVP)
WS:   1.24 mg/L (source: WSKOWWIN)
```

```
Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used:  5.34  (user entered)
Log Kaw used:  -5.401  (HenryWin est)
Log Koa (KOAWIN v1.10 estimate):  10.741
Log Koa (experimental database):  None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model)         :   0.1351
Biowin2 (Non-Linear Model)     :   0.0059
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model):   2.2563  (weeks-months)
Biowin4 (Primary Survey Model) :   3.1916  (weeks       )
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model)    :  -0.0966
Biowin6 (MITI Non-Linear Model):   0.0071
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -1.1381
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):  0.00399 Pa (2.99E-005 mm Hg)
Log Koa (Koawin est  ): 10.741
Kp (particle/gas partition coef. (m3/ug)):
Mackay model           :  0.000753
Octanol/air (Koa) model:  0.0135
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model     :  0.0265
Mackay model           :  0.0568
Octanol/air (Koa) model:  0.52

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 125.6992 E-12 cm3/molecule-sec
Half-Life =     0.085 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =     1.021 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.0416 (Junge-Pankow, Mackay avg)
0.52 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc    :  3.401E+004  L/kg (MCI method)
Log Koc:  4.532       (MCI method)
Koc    :  6195  L/kg (Kow method)
Log Koc:  3.792       (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 = 3.190 (BCF = 1550 L/kg wet-wt)
```

Log Biotransformation Half-life (HL) = 0.1856 days (HL = 1.533 days)
Log BCF Arnot-Gobas method (upper trophic) = 2.777 (BCF = 598.6)
Log BAF Arnot-Gobas method (upper trophic) = 2.789 (BAF = 614.6)
log Kow used: 5.34 (user entered)

Volatilization from Water:
Henry LC: 9.72E-008 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 1.051E+004 hours (438 days)
Half-Life from Model Lake : 1.148E+005 hours (4785 days)

Removal In Wastewater Treatment:
Total removal: 85.90 percent
Total biodegradation: 0.73 percent
Total sludge adsorption: 85.17 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	**0.0625**	**2.04**	**1000**
Water	**12**	**900**	**1000**
Soil	**65**	**1.8e+003**	**1000**
Sediment	**22.9**	**8.1e+003**	**0**

Persistence Time: 1.42e+003 hr

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

Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	0.0625	2.04	1000
Water	12	900	1000
water	(11.3)		
biota	(0.124)		
suspended sediment	(0.578)		
Soil	65	1.8e+003	1000
Sediment	22.9	8.1e+003	0

Persistence Time: 1.42e+003 hr

Level III Fugacity Model: (EQC Default)

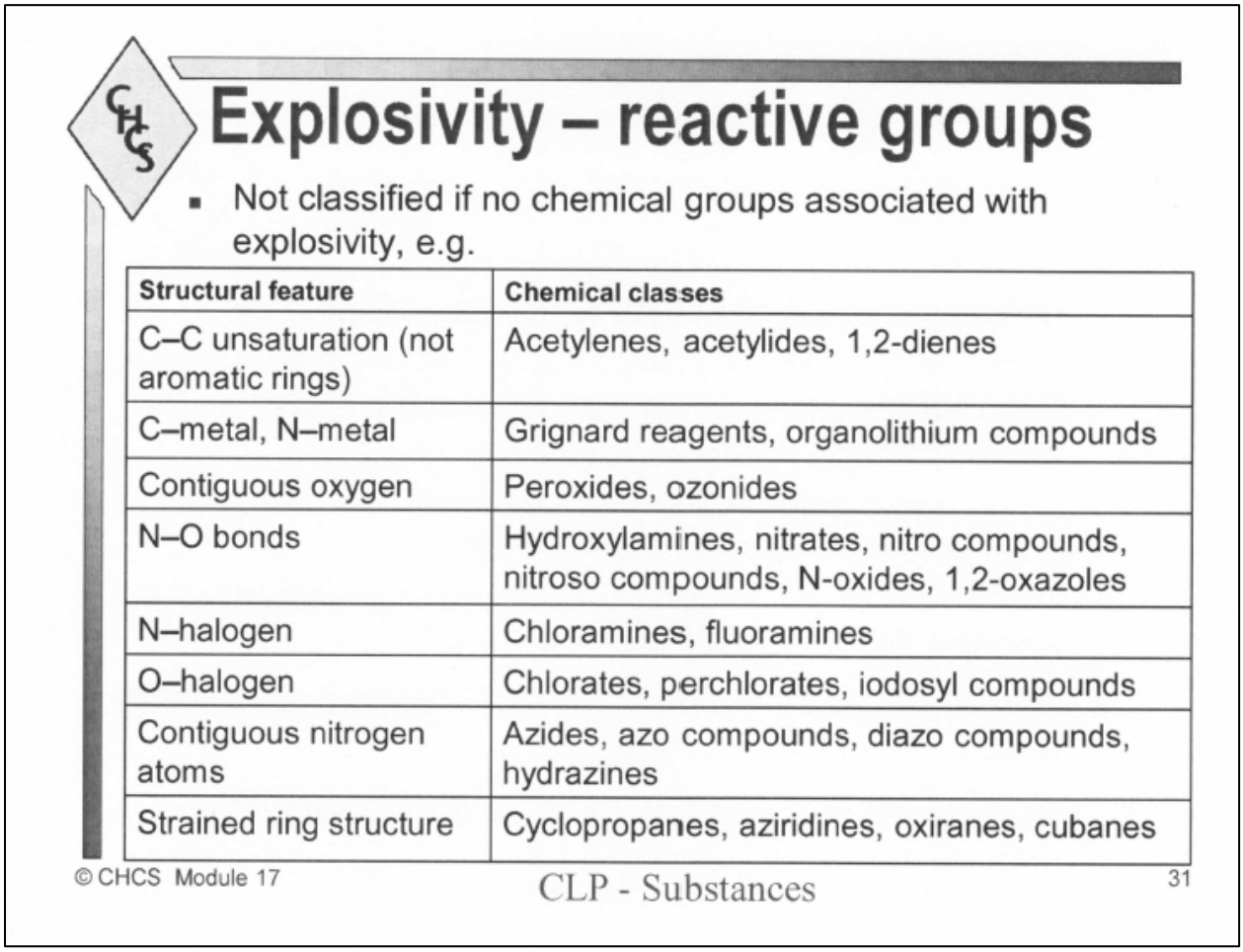
Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	0.0502	2.04	1000
Water	8.42	900	1000
water	(7.35)		
biota	(0.0804)		
suspended sediment	(0.989)		
Soil	52.2	1.8e+003	1000
Sediment	39.3	8.1e+003	0

Persistence Time: 1.76e+003 hr

....

APPENDIX I: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

- Not classified if no chemical groups associated with explosivity, e.g.

Structural feature	Chemical classes
C–C unsaturation (not aromatic rings)	Acetylenes, acetylides, 1,2-dienes
C–metal, N–metal	Grignard reagents, organolithium compounds
Contiguous oxygen	Peroxides, ozonides
N–O bonds	Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles
N–halogen	Chloramines, fluoramines
O–halogen	Chlorates, perchlorates, iodosyl compounds
Contiguous nitrogen atoms	Azides, azo compounds, diazo compounds, hydrazines
Strained ring structure	Cyclopropanes, aziridines, oxiranes, cubanes

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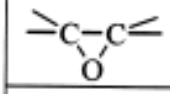
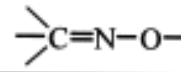
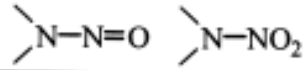
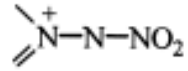
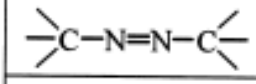
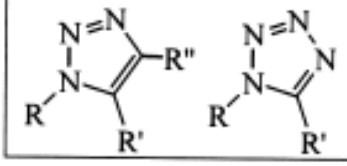
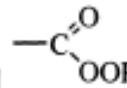
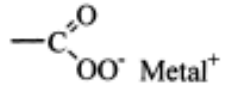
Explosivity – Full List

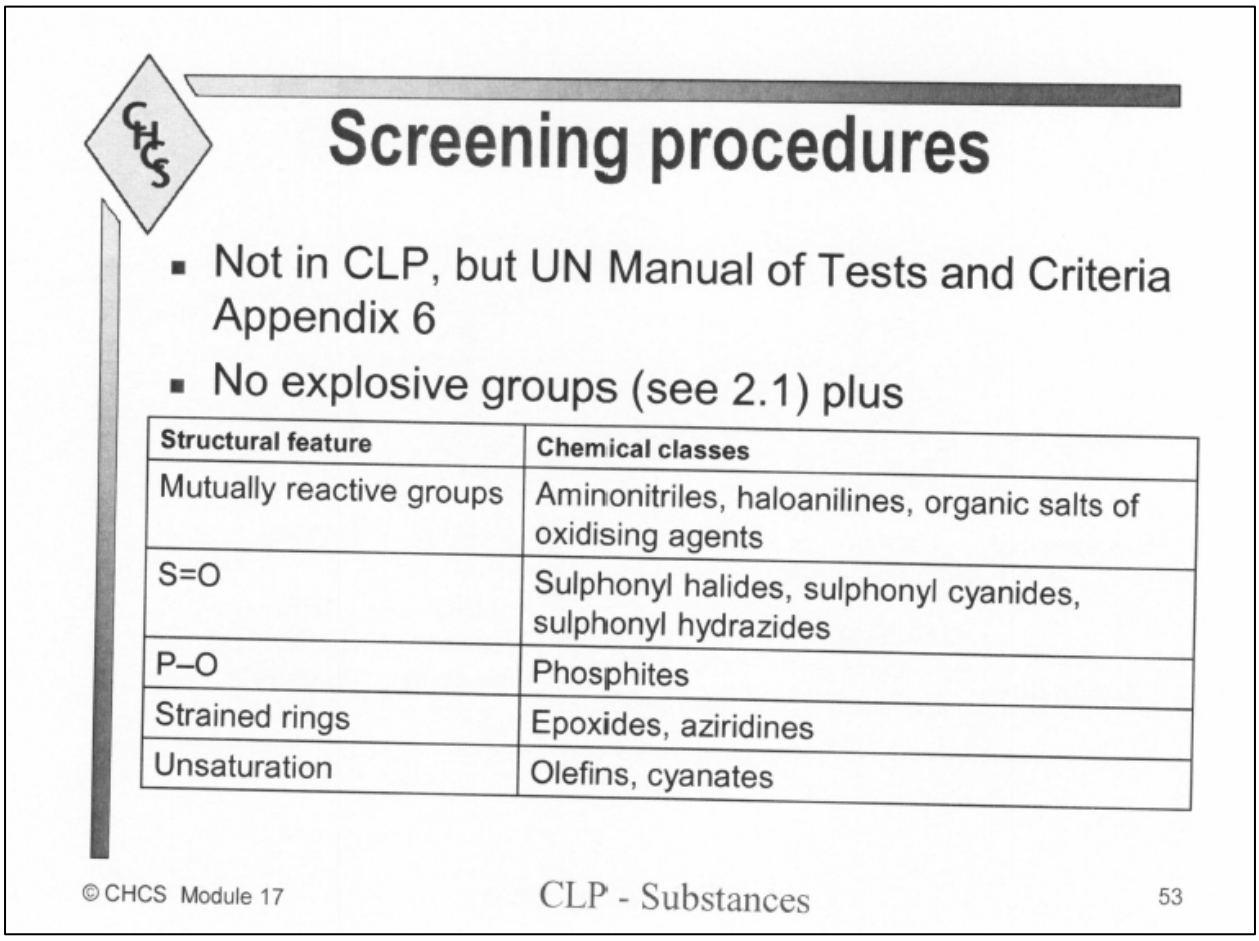
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or *aci*-Nitro Salts
	N-Metal Derivatives (especially heavy metals)
	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. $NC1_3$, $RNC1_2$	N-Halogen Compounds

Adapted from Bretherick (Bretherick's Handbook of Reactive Chemical Hazards 6th Ed., 1999, Butterworths, London)

Self-Reactive Substances



APPENDIX J: Change in Benchmark Score

Table 6 provides a summary of changes to the GreenScreen® Benchmark™ for 77PPD. This GreenScreen® assessment has undergone one round of updates without affecting the benchmark score.

Table 6: Change in GreenScreen® Benchmark™ for 77PPD

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
October 19, 2021	BM-2	v. 1.4	New assessment
November 9, 2021	BM-2	v. 1.4	Minor updates

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