N,N'-DICYCLOHEXYL-4-PHENYLENEDIAMINE (CCPD)

(CAS #4175-38-6)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 5, 2021

ToxServices Review Date: November 5, 2026[1]

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[1] Although CPA's Assessment Expiration Policy (CPA 2018a) indicates that Benchmark 1 assessments have no expiration date, ToxServices strives to review BM-1s in a five-year period to ensure currency of data presented in the BM-1 GreenScreen® assessments.

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for N,N'-Dicyclohexyl-4-phenylenediamine (CCPD) (CAS #4175-38-6)

Although no specific uses for N,N'-Dicyclohexyl-4-phenylenediamine (CCPD) were identified, based on similarity to other phenylenediamines, it is presumed to be used as an antioxidant / antiozonant, fuel additive, and in monomer distillation. CCPD is predicted to be a solid at room temperature. Based on its predicted high boiling point and low vapor pressure, it is not expected to be a volatile chemical. It has predicted low water solubility, and its modeled log K_{ow} indicates a potential to bioaccumulate.

CCPD was assigned a **GreenScreen Benchmark™ Score of 1** ("Avoid – Chemical of High Concern"). This score is based on the following hazard score combinations:

- Benchmark 1a
    - High Persistence-P + High Bioaccumulation-B + Very High Ecotoxicity (acute aquatic toxicity-AA, chronic aquatic toxicity-CA)
    - High P + High B + Very High Group II Human Toxicity (skin irritation-IrS)
    - High P + High B + High Group II* Human Toxicity (systemic toxicity repeated dose-STr* and skin sensitization-SnS*)

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

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for endocrine activity, respiratory sensitization, aquatic toxicity, persistence and bioaccumulation, and *in vitro* testing for genotoxicity. 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 CCPD's NAMs dataset include the lack of sufficient data on endocrine activity, respiratory sensitization, aquatic toxicity, persistence, and bioaccumulation, along with a lack of validated test methods for respiratory sensitization. CCPD's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays in mimicking *in vivo* metabolic systems, the uncertain *in vivo* relevance of *in silico* modeling of endocrine receptor binding, the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization, and the lack of guidance from the ECHA framework to subclassify respiratory sensitizers to Category 1A and 1B. Some of CCPD'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 CCPD

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	*H*		*H*	*L*	DG	*H*	*M*	*vH*	*H*	*vH*	*vH*	*H*	*H*	*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'-Dicyclohexyl-4-phenylenediamine (CCPD) (CAS #4175-38-6)

Method Version: GreenScreen® Version 1.4
Assessment Type[2]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Megan B. Boylan, M.S.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 18, 2021, November 3, 2021

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Name: Bingxuan Wang, Ph.D., D.A.B.T.
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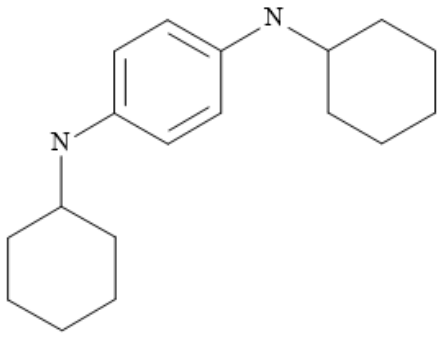
Organization: ToxServices LLC
Date: October 19, 2021, November 5, 2021

ToxServices Review Date: November 5, 2026[3]

Chemical Name: N,N'-Dicyclohexyl-4-phenylenediamine (CCPD)

CAS Number: 4175-38-6

Chemical Structure(s):

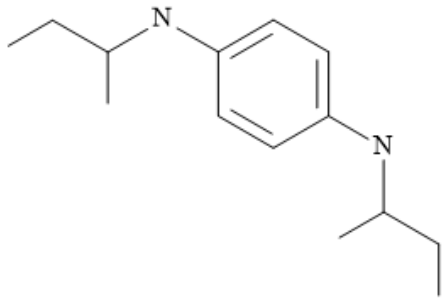


Also called: 1,4-Benzenediamine, N,N'-dicyclohexyl-; N,N'-dicyclohexyl-1,4-phenylenediamine; N,N'-Dicyclohexyl-p-phenylenediamine; 1,4-Benzenediamine, N1,N4-dicyclohexyl- (ChemIDplus 2021).

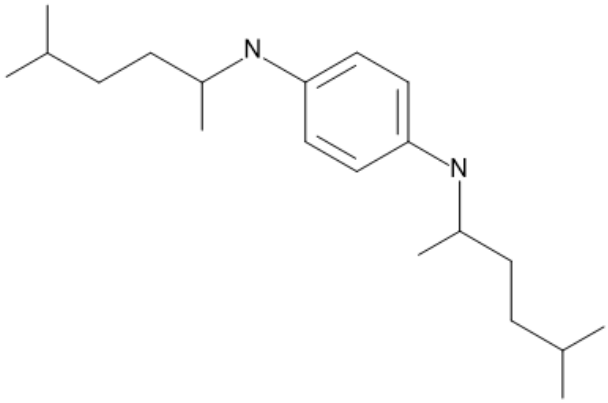
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
There were insufficient data available to evaluate the toxicity of CCPD. ToxServices identified N,N'-di-sec-butyl-p-phenylenediamine (44PD) (CAS #101-96-2) and N,N'-bis(1,4-dimethylpentyl)-p-phenylenediamine (77PPD) (CAS #3081-14-9) as surrogates, as all compounds are alkyl substituted phenylenediamine compounds, which have been evaluated as a class by the United States environmental Protection Agency (U.S. EPA) (2011). 44PD and 77PPD have maximum common substructure (MCS) Tanimoto coefficients of 0.8000, and 0.7500, respectively, with the target compound (ChemMine 2021), indicating appropriate structural similarities. ToxServices considers 44PD to be a stronger surrogate for human health and ecotoxicity endpoints than 77PPD as the alkyl substituents on 44PD (i.e., C4) is

[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[3] Although CPA's Assessment Expiration Policy (CPA 2018a) indicates that Benchmark 1 assessments have no expiration date, ToxServices strives to review BM-1s in a five-year period to ensure currency of data presented in the BM-1 GreenScreen® assessments.

smaller than the cyclohexane substituent (C6) in the target chemical, while the alkyl substituents on 77PPD (C7) is slightly larger than the C6 in the target chemical. Therefore, where data are available and sufficient for the stronger surrogate, data on the weaker surrogate are not described. For persistence, 77PPD is considered a conservative surrogate for the target compound as it is slightly larger and hence likely takes longer to degrade. However, as the alkyl substituents in the target compound is cyclic while they are open chains in the surrogates, ToxServices considers both chemicals weak surrogates.



Surrogate: 44PD (CAS #101-96-2)



Surrogate: 77PPD (CAS #3081-14-9)

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

Known Impurities[4]:
No information is available. The screen is performed on the theoretical pure substance.

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

GreenScreen® Summary Rating for CCPD[5,6 7,8]: CCPD was assigned a **GreenScreen Benchmark™ Score of 1** ("Avoid – Chemical of High Concern") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 1a
  - High Persistence-P + High Bioaccumulation-B + Very High Ecotoxicity (acute aquatic toxicity-AA, chronic aquatic toxicity-CA)
  - High P + High B + Very High Group II Human Toxicity (skin irritation-IrS)
  - High P + High B + High Group II* Human Toxicity (systemic toxicity repeated dose-STr* and skin sensitization-SnS*)

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

Figure 1: GreenScreen® Hazard Summary Table for CCPD

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

Using OECD Toolbox, ToxServices predicted there would be no hydrolysis products (OECD 2021). ToxServices identified no other feasible and/or relevant environmental transformation products for CCPD.

Introduction

Although no specific uses for CCPD were identified, based on similarity to other phenylenediamines, it is presumed to be used as an antioxidant / antiozonant, fuel additive, and in monomer distillation.

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

[5] 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.
[6] See Appendix A for a glossary of hazard endpoint acronyms.
[7] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[8] 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.

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 2021). 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).

CCPD is not listed on the U.S. EPA 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),[9] 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 CCPD can be found in Appendix C.

- CCPD is an LT-U chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- CCPD is not listed on the U.S. DOT list.
- CCPD is not on any GreenScreen®-specified lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

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 CCPD, as indicated in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 1: GHS H Statements for CCPD) (CAS #4175-38-6)

H Statement	H Statement Details
No harmonized GHS H statements are reported by the European Chemicals Agency (ECHA). According to the notifications provided by companies to ECHA in REACH registrations, no hazards have been classified.	

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for CCPD (CAS #4175-38-6)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
None identified		None identified	

Physicochemical Properties of CCPD

CCPD is expected to be a solid at room temperature. Based on its estimated high boiling point and low vapor pressure, it is not expected to be a volatile chemical. It is estimated to have a low water solubility, and its modeled log K_{ow} suggests a bioaccumulation potential if not considering metabolism.

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

Table 3: Physical and Chemical Properties of CCPD (CAS #4175-38-6)		
Property	**Value**	**Reference**
Molecular formula	$C_{18}H_{28}N_2$	ChemIDplus 2021
SMILES Notation	C1CCC(CC1)Nc2ccc(NC3CCCCC3)cc2	ChemIDplus 2021
Molecular weight	272.433 g/mol	ChemIDplus 2021
Physical state	N/A	
Appearance	N/A	
Melting point	131.43°C (estimated)	U.S. EPA 2017a
Boiling point	379.45°C (estimated)	U.S. EPA 2017a
Vapor pressure	2.24 x 10^{-6} mm Hg @ 25°C (estimated)	U.S. EPA 2017a
Water solubility	0.5896 mg/L @ 25°C (estimated)	U.S. EPA 2017a
Dissociation constant	N/A	
Density/specific gravity	N/A	
Partition coefficient	log K_{ow} = 5.24 (estimated)	U.S. EPA 2017a

Toxicokinetics
No toxicokinetic data were found for CCPD.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

- 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
  - *Surrogate: 77PPD (CAS #3081-14-9):* 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 (Klimisch 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*
CCPD was assigned a score of Low for mutagenicity/genotoxicity based on negative results in an *in vitro* bacterial reverse mutation assay, mammalian cell mutation assay, and an *in vitro* chromosomal

aberration assay for a surrogate. 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 low as it is based on data for a weak surrogate.

- 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 2021b
  - *In vitro: Surrogate: 44PD (CAS #101-96-2):* Negative results for mutagenicity were obtained in an Ames reverse mutation assay conducted according to Ames et al. (1975) methods (GLP compliance not reported). *Salmonella typhimurium* test strains TA97, TA98, TA100, and TA1535 were exposed to 44PD (>82% purity) in dimethyl sulfoxide (DMSO) at concentrations of 0.33-333 µg/plate both in the presence and absence of metabolic activation. No increases in the mutation frequency were observed in the presence and absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vitro: Surrogate: 44PD (CAS #101-96-2):* Negative results for mutagenicity were obtained in a GLP-compliant mammalian cell mutation assay conducted according to OECD Guideline 476/EPA OPPTS 870.5300. Chinese hamster lung fibroblasts (V79) were exposed to 44PD (purity not reported) in DMSO at concentrations up to 8.50 µg both in the presence and absence of metabolic activation. No increases in the mutation frequency were observed in the presence and absence of metabolic activation (Klimisch 1, reliable without restriction).
  - *In vitro: Surrogate: 44PD (CAS #101-96-2):* Negative results for clastogenicity were obtained in a GLP-compliant chromosomal aberration assay conducted according to OECD Guideline 473/EPA OPPTS 870.5375. Chinese hamster lung fibroblasts (V79) were exposed to 44PD (98% purity) in DMSO at concentrations up to 8.50 µg/mL both in the presence and absence of metabolic activation. No increases in the induction of chromosomal aberrations were seen at any dose level either in the presence or absence of metabolic activation (Klimisch 1, reliable without restriction).

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

CCPD was assigned a score of Low for reproductive toxicity based on a lack of reproductive toxicity in a GLP-compliant 3-generation oral study in rats for the surrogate 77PPD, supported by a lack of reproductive toxicity up to the highest tested dose of 60 mg/kg/day for the surrogate 4PPD in an OECD 421 screening 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 low as it is based on data for weak surrogates.

- 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 2021b
  - *Surrogate: 44PD (CAS #101-96-2): Oral:* A GLP-compliant OECD Guideline 421/EPA OPPTS 870.3550 reproduction/developmental toxicity screening test was performed with Wister Han rats (10/sex/dose) administered gavage doses of the test compound (96.09% purity) in polyethylene glycol (PEG)-400 at 0, 10, 30, and 60 mg/kg/day. Male animals were treated for 29 days, up to and including the day before necropsy; this included a minimum of 14 days prior to mating and during the mating period. Female animals that delivered were treated for 50-54 days, including 14 days prior to mating, conception, the

duration of pregnancy, and at least 14 days after delivery up to the day before necropsy. Parental animals were evaluated for clinical signs of toxicity, estrous cyclicity, litter observations, gross pathology, reproductive indices, and offspring viability indices. There were no treatment-related effects on estrous cyclicity, mating index, precoital time, number of implantation sites, fertility index, gestation index and duration, parturition, litter size, live birth and viability indices, lactation index, reproductive organs, and reproductive performance. Based on the lack of effects, a reproductive NOAEL of 60 mg/kg/day was established (Klimisch 1, reliable without restriction).

- ECHA 2021a
    - *Surrogate: 77PPD (CAS #3081-14-9): Oral:* 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 (Klimisch 2, reliable with restrictions).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
CCPD was assigned a score of Moderate for developmental toxicity based on increased resorptions in the presence of maternal toxicity in a prenatal developmental toxicity study for the surrogate 44PD. Further, reduced pup body weights and survival to weaning were reported in a 3-generation oral study in rats at a dose causing maternal systemic toxicity for the surrogate 77PPD. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicities in animals (CPA 2018b). The confidence in the score is low as it is unclear if the developmental effects observed are secondary to maternal toxicity, and the surrogates are weak.

- 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 2021b
    - *Surrogate: 44PD (CAS #101-96-2): Oral:* In a GLP-compliant developmental toxicity study conducted according to OECD Guideline 414/EU Method B.31/EPA OPPTS 870.3700, pregnant Wister Han rats (22/dose) received doses of 10, 30, and 60 mg/kb/ 44PD (96.09% purity) in polyethylene glycol (PEG)-400 by gavage on gestation days (GD) 6-20. Parameters evaluated include clinical observations, body weight, food consumption, ovaries and uterine content, and fetal examinations. There was a dose-related increase in mean liver weight and liver to body weight ratio, as well as an increase in resorptions in high-dose animals. There were no treatment-related effects on developmental parameters. Therefore, a maternal NOAEL of 30 mg/kg/day and a fetal NOAEL of 60 mg/kg/day were established (Klimisch 1, reliable without restriction).
- 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).
    - *Surrogate: 77PPD (CAS #3081-14-9):* 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) (Klimisch 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.*
    - *Surrogate: 77PPD (CAS #3081-14-9):* 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 (Klimisch 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.*

- *Surrogate: 77PPD (CAS #3081-14-9):* 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 (Klimisch 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

CCPD was assigned a score of Data Gap for endocrine activity based on insufficient data. *In silico* modeling results are mixed, and no measured data 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.

- DTU 2021 (only results that are in domain are described below)
    - CCPD is predicted to be positive for estrogen receptor α binding (full and balanced training set, human *in vitro*) by the SciQSAR model (Appendix D).
    - CCPD is predicted to be negative for estrogen receptor α activation (human *in vitro* and CERAPP data *in vitro*) by the Leadscope model (Appendix D).
    - CCPD is predicted to be negative for androgen receptor inhibition (Human *in vitro*) by the model battery consisting of negative and in domain predictions by Case Ultra, Leadscope and SciQSAR (Appendix D).
    - CCPD is predicted to be negative for androgen receptor activation with CoMPARA data (*in vitro*) by the Leadscope model (Appendix D).
    - CCPD is predicted to be positive for thyroperoxidase (TPO) inhibition by the QSAR 1 (rat *in vitro*) model in Leadscope (Appendix D).

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): *H*

CCPD was assigned a score of High for acute toxicity based on oral LD_{50} values of 222-271 mg/kg and dermal LD_{50} values of 756-2,806 mg/kg for a structural surrogate. GreenScreen® criteria classify chemicals as a High hazard for acute toxicity when oral LD_{50} values are >50-300 mg/kg and dermal LD_{50} values are >200-1,000 mg/kg (CPA 2018b). The confidence in the score is low as it is based on data for a weak surrogate.

- 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 2021b
    - *Surrogate: 44PD (CAS #101-96-2): Oral*: LD_{50} = 271 mg/kg bw, GLP-compliant, no guideline followed, Sprague-Dawley rat, male and female (Klimisch 2, reliable with restrictions).
    - *Surrogate: 44PD (CAS #101-96-2): Oral*: LD_{50} = 222 mg/kg bw, GLP-compliant, no guideline followed, Sprague-Dawley rat, male and female (Klimisch 2, reliable with restrictions).
    - *Surrogate: 44PD (CAS #101-96-2): Dermal*: LD_{50} = 756 mg/kg bw, non-GLP compliant, OECD Guideline 402, Wistar rat, male and female (Klimisch 2, reliable with restrictions).
    - *Surrogate: 44PD (CAS #101-96-2): Dermal*: LD_{50} = 2,806 mg/kg bw, GLP-compliant, no guideline followed, New Zealand white rabbit, male and female (Klimisch 2, reliable with restrictions).

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

CCPD was assigned a score of Data Gap due to insufficient data available. In the acute oral and dermal toxicity studies on the surrogate 44PD, it was not clear if the effects reported occurred in animals that died or survived. In the acute oral and dermal toxicity studies on the surrogate 77PPD, there were no indications of systemic effects at sub-lethal doses. However, as 44PD appears to be more toxic than 77PPD, and the target chemical may be more toxic than 77PPD, ToxServices assigned a Data Gap for this endpoint.

- 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 2021b
  - *Surrogate: 44PD (CAS #101-96-2): Oral*: A GLP-compliant study was conducted according to no specific guidelines where male and female Sprague-Dawley rats (5/sex/dose) received 44PD (96.09% purity) in corn oil via gavage at 200, 313, 490, 767, and 1,200 mg/kg. Clinical signs including lethargy, ataxia, ptosis, and green and/or red/brown colored urine were observed. Most animals experiencing lethargy, ptosis, ataxia, prostration and/or lacrimation died subsequently. Necropsy revealed that gastrointestinal toxicity was the likely cause of lethality, including inflammation and hemorrhage. The authors established an LD_{50} of 271 mg/kg (Klimisch 2, reliable with restrictions).
  - *Surrogate: 44PD (CAS #101-96-2): Oral*: A GLP-compliant study was conducted according to no specific guidelines where male and female Sprague-Dawley rats (5/sex/dose) received 44PD (96.09% purity) in corn oil via gavage at 200, 263, 346, 456, and 600 mg/kg. Clinical signs including lethargy, ataxia, prostration, salivation, ptosis, and green or red colored urine were observed. Every animal that had red urine died during the observation period All animals experiencing ataxia and prostration also died subsequently. Necropsy of dead animals revealed gastrointestinal inflammation, hemorrhage, and/or distension, green material in the urinary bladder/green staining on the fur, off-white hepatic coloration, while foci on hepatic lobes, hemorrhaged diaphragms, brown/or clear fluid in the thoracic cavity, red fluid in the urinary bladder, and dark adrenals. The authors established an LD_{50} of 222 mg/kg (Klimisch 2, reliable with restrictions).
  - *Surrogate: 44PD (CAS #101-96-2): Dermal*: A non-GLP compliant study was conducted according to OECD Guideline 402 where male and female Wistar rats (5/sex/dose) received 44PD (98% purity) in carboxymethylcellulose (CMC) was applied at 316, 562, 825, and 1,210 mg/kg under occlusive conditions. Mortality was observed at doses of 562 mg/kg and above. Clinical signs including dyspnea, apathy, trembling and poor general state were seen starting on day 1, as well as deep skin necrosis starting on day 7 and edema starting on day 1. Mean body weight increased over the study period. There were no necropsy findings in survivors, other than local effects on the skin including extensive necrosis. Authors established an LD_{50} of 756 mg/kg (Klimisch 2, reliable with restrictions).
  - *Surrogate: 44PD (CAS #101-96-2): Dermal*: A GLP-compliant study was conducted according to no specific guidelines where male and female New Zealand white rabbits (4/sex/dose) received 44PD (96.09% purity) unchanged at 2,500, 3,536, and 5,000 mg/kg under occlusive conditions. Mortality was observed at the two higher dose levels. Clinical signs including lethargy, ataxia, prostration, partial loss of the ability to move the limbs, and green coloration were seen. Most of the animals with clinical signs of systemic toxicity died during the observation period. Erythema and edema were seen through the second day after treatment to the end of the observation period. Three of the 6 survivors lost weight during the first week of observation but gained weight during the subsequent week. The authors established an LD_{50} of 2,806 mg/kg (Klimisch 2, reliable with restrictions).
- 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 (Klimisch 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 (Klimisch 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 (Klimisch 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 (Klimisch 2, reliable with restrictions).

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

CCPD was assigned a score of High for systemic toxicity (repeated dose) based on 28-day LOAELs of 10 mg/kg/day for the surrogate 44PD, which warrants GHS Category 1 classification. The other surrogate 77PPD is less toxic, and the 90-day and 28-day oral studies warrant GHS Category 2 classification. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when data meet GHS Category 1 classification criteria (CPA 2018b). The confidence in the score is low as it is based on data for a weak surrogate.

- 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 2021b
  - <u>*Surrogate: 44PD (CAS #101-96-2)*</u>: *Oral:* A GLP-compliant subacute feeding study was conducted according to OECD Guideline 407/EC Guideline 84/449/EC. Male and female Wistar rats (5/sex/dose) were administered doses of 44PD (98.8% purity) in polyethylene glycol(PEG)-400 of 3, 10, and 30 mg/kg/day for four weeks. Parameters evaluated include

clinical observations, body weight, food and water consumption, ophthalmoscopic examinations, hematology, clinical chemistry, gross pathology, and histopathology. High-dose females showed an increased incidence of focal alopecic areas and sparsely haired regions. Mid- and high-dose females had increased plasma concentrations of both glucose and albumin; additionally, high-dose females also had increased levels of CGT activity, total protein, bilirubin, cholesterol, and calcium. There was an increase in the absolute and relative weights of the liver in both high-dose males and females, along with an increase in relative kidney weights in high-dose females. There were clear histological changes in the livers of mid- and high-dose male and female animals. Based on these effects, a NOAEL of 3 mg/kg/day was established (Klimisch 1, reliable without restriction). *The LOAEL of 10 mg/kg/day is below the duration-adjusted GHS Category 1 cutoff of 30 mg/kg/day (i.e., 10 mg/kg/day x 90 days/30 days = 30 mg/kg/day). Therefore, the test substance is classified to GHS Category 1.*

- *Surrogate: 44PD (CAS #101-96-2)*: *Oral:* In a non-GLP, non-guideline study, rats (strain not specified, 6/sex/dose)) were exposed to the test substance (purity not reported) in the feed at 0, 0.002% (increased to 0.1% after 56 days and then 0.2% after another 25 days), 0.01% or 0.05% for 3 months. Parameters evaluated include body weight, food consumption, hematology, clinical chemistry, organ weights, and histopathology. Rats of both sexes at 0.05% had depressed growth. Similar growth effects were observed in the 0.002% group when the dose was increased. There were no other changes in the parameters measured. ECHA authors identified a NOEL of 5.4 mg/kg (100 ppm) based on lack of effects found (Klimisch 2, reliable with restrictions). *ToxServices identified a LOEL of 500 ppm (27 mg/kg) based on reduced growth.*
- *Surrogate: 44PD (CAS #101-96-2)*: *Oral:* In a GLP-compliant non-guideline subacute toxicity study, Sprague-Dawley rats (10/sex/dose) received the test substance (purity 97.0%) by gavage in corn oil at 0, 10, 25, 50 or 100 mg/kg/day for 28 days. Evaluations included case side observation, clinical observation, body weight, food consumption, hematology, clinical chemistry, gross pathology, and histopathology. Feed consumption transiently decreased at the high dose in both sexes. Two deaths at the high dose were judged by the study authors to be attributable to the treatment. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and serum gamma glutamyl transpeptidase (GGTP) were significantly increased in high dose animals of both sexes, and SGOT and SGPT levels were both increased in males at 50 mg/kg/day and the GGTP level was increased in females at this dose. There were slight increases of SGOT and SGPT at the low dose. These erythropoietic parameter changes indicated a trend to anemia but the evidence is weak. There was a significant increase in absolute and relative liver weight at 25 mg/kg/day and above in both sexes. Histopathological examination revealed increased hepatocellular lesions at all dose levels (mainly periportal degeneration and necrosis with dose-dependent severity). Study authors did not identify a NOAEL for this study (Klimisch 2, reliable with restrictions). *ToxServices identified a LOAEL of 10 mg/kg/day based on histopathological changes in the liver observed even at the lowest dose level. The LOAEL of 10 mg/kg/day is below the duration-adjusted GHS Category 1 cutoff of 30 mg/kg/day (i.e., 10 mg/kg/day x 90 days/30 days = 30 mg/kg/day). Therefore, the test substance is classified to GHS Category 1.*

- ECHA 2021a, U.S. EPA 2011
  - *Surrogate: 77PPD (CAS #3081-14-9):* *Oral:* 77PPD was evaluated in a GLP-compliant sub-chronic 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) (Klimisch 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.*

- <u>*Surrogate: 77PPD (CAS #3081-14-9):*</u> *Oral:* 77PPD was evaluated in a GLP-compliant sub-acute 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 not 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 (Klimisch 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 * 90days/28days, and ≤ 100 mg/kg/day * 90days/28days). Therefore, the LOAEL of 91.30 mg/kg/day meets the criteria for GHS Category 2.*

- *Surrogate: 77PPD (CAS #3081-14-9): 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 (Klimisch 2, reliable with restrictions).

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

CCPD was assigned a score of Low for neurotoxicity (single dose) based on the lack of clinical signs or necropsy findings indicative of neurotoxicity at sublethal doses with the surrogate 44PD. 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, and data are available for a weak surrogate.

- 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 2021b
  - *Surrogate: 44PD (CAS #101-96-2): Oral*: A GLP-compliant study was conducted according to no specific guidelines where male and female Sprague-Dawley rats (5/sex/dose) received 44PD (96.09% purity) in corn oil via gavage at 200, 313, 490, 767, and 1,200 mg/kg. Clinical signs including lethargy, ataxia, ptosis, and green and/or red/brown colored urine were observed. Most animals experiencing lethargy, ptosis, ataxia, prostration and/or lacrimation died subsequently. Necropsy revealed that gastrointestinal toxicity was the likely cause of lethality, including inflammation and hemorrhage. The authors established an LD_{50} of 271 mg/kg (Klimisch 2, reliable with restrictions).
  - *Surrogate: 44PD (CAS #101-96-2): Oral*: A GLP-compliant study was conducted according to no specific guidelines where male and female Sprague-Dawley rats (5/sex/dose) received 44PD (96.09% purity) in corn oil via gavage at 200, 263, 346, 456, and 600 mg/kg. Clinical signs including lethargy, ataxia, prostration, salivation, ptosis, and green or red colored urine were observed. Every animal that had red urine died during the observation period All animals experiencing ataxia and prostration also died subsequently. Necropsy of dead animals revealed gastrointestinal inflammation, hemorrhage, and/or distension, green material in the urinary bladder/green staining on the fur, off-white hepatic coloration, while foci on hepatic lobes, hemorrhaged diaphragms, brown/or clear fluid in the thoracic cavity, red fluid in the urinary bladder, and dark adrenals. The authors established an LD_{50} of 222 mg/kg (Klimisch 2, reliable with restrictions).
  - *Surrogate: 44PD (CAS #101-96-2): Dermal*: A non-GLP compliant study was conducted according to OECD Guideline 402 where male and female Wistar rats (5/sex/dose) received 44PD (98% purity) in carboxymethylcellulose (CMC) was applied at 316, 562, 825, and 1,210 mg/kg under occlusive conditions. Mortality was observed at doses of 562 mg/kg and above. Clinical signs including dyspnea, apathy, trembling and poor general state were seen starting on day 1, as well as deep skin necrosis starting on day 7 and edema starting on day 1.

Mean body weight increased over the study period. There were no necropsy findings in survivors, other than local effects on the skin including extensive necrosis. Authors established an LD_{50} of 756 mg/kg (Klimisch 2, reliable with restrictions).

- *Surrogate: 44PD (CAS #101-96-2): Dermal*: A GLP-compliant study was conducted according to no specific guidelines where male and female New Zealand white rabbits (4/sex/dose) received 44PD (96.09% purity) unchanged at 2,500, 3,536, and 5,000 mg/kg under occlusive conditions. Mortality was observed at the two higher dose levels. Clinical signs including lethargy, ataxia, prostration, partial loss of the ability to move the limbs, and green coloration were seen. Most of the animals with clinical signs of systemic toxicity died during the observation period. Erythema and edema were seen through the second day after treatment to the end of the observation period. Three of the 6 survivors lost weight during the first week of observation but gained weight during the subsequent week. The authors established an LD_{50} of 2,806 mg/kg (Klimisch 2, reliable with restrictions).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
CCPD was assigned a score of Data Gap for neurotoxicity (repeated dose) based on the lack of available 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.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): *H*
CCPD was assigned a score of High for skin sensitization based on positive results in an open epicutaneous assay in rabbits leading to a GHS Category 1A classification for the surrogate 44PD (CAS #101-96-2). GreenScreen® criteria classify chemicals as a High hazard for skin sensitization when classified as Category 1A (CPA 2018b). The confidence in the score is low as it is based on reliable experimental data for a weak surrogate.

- 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 2021b
  - *Surrogate: 44PD (CAS #101-96-2):* In a GLP-compliant open epicutaneous assay conducted according to Klecak (1977), 44PD (96.92% purity) was applied to female Dunkin Hartley guinea pigs (8/dose) at 0.1, 0.3, 1, and 3% in ethanol under epicutaneous open conditions; the challenge doses were also done at 0.1, 0.3, 1, and 3% in ethanol under epicutaneous open conditions. There was a dose-response in reactions, with up to 100% of animals having a positive response even with 0.1% induction dose. Therefore, the authors classified 4PPD as a GHS Category 1 sensitizer (Klimisch 2, reliable with restrictions).
    - Based on 100% of the animals responding following an induction dose of 0.1%, 44PD warrants classification as a GHS Category 1A skin sensitizer. GHS criteria define Category 1A skin sensitizers as chemicals that produce positive reactions in ≥ 15% animals at ≤ 0.2% topical induction doses (UN 2021).

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

CCPD was assigned a score of Moderate for respiratory sensitization based on positive skin sensitization results for a surrogate and the presence of a structural alert for respiratory sensitization. GreenScreen® criteria classify chemicals as a Moderate hazard for respiratory sensitization when there is low to moderate frequency of concern (GHS Category 1B) (CPA 2018b). Confidence in the score is reduced as there are no data to subclassify the compound to Category 1A and 1B, which translate to Moderate and High scores, respectively.

- 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
  - CCPD contains a structural alert for respiratory sensitization: Pro-Michael Addition (Appendix E)
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of CCPD according to ECHA's guideline (ECHA 2017), which states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). CCPD contains a structural alert for respiratory sensitization and is expected to be a skin sensitizer based on positive experimental data for a structural surrogate. According to the ECHA guidance, this warrants classification as a GHS Category 1 respiratory sensitizer. However, ECHA did not provide guidance on subcategorization to GHS Category 1A (high potency) and 1B (low potency). Due to the lack of specific respiratory sensitization data, ToxServices classified it to GHS Category 1B with low confidence.

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

CCPD was assigned a score of Very High for skin irritation/corrosivity based on corrosive effects seen in rabbits in two studies for the surrogate 44PD. GreenScreen® criteria classify chemicals as a Very High hazard for skin irritation/corrosivity when they are classified as GHS Category 1 (corrosive) (CPA 2018b). The confidence in the score is low as it is based on reliable studies for a weak surrogate.

- 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 2021b
  - *Surrogate: 44PD (CAS #101-96-2):* In a GLP-compliant skin irritation study conducted according to Department of Hazardous Materials Regulations of the CFR, Title 49, Section 173.240, male and female New Zealand albino rabbits (3/sex) were administered undiluted 44PD at 0.5 mL on shaved skin for 4 hours under occlusive conditions. Skin was observed at 4 hours, 24 hours, 48 hours, 72 hours, 1 week, and 2 weeks following treatment. Gross observations of corrosion were seen in 2 of 6 rabbits at the 1 week observation reading, and 4 of 6 rabbits at the 2-week reading. A corrosive material is defined as one that causes alteration or tissue destruction to intact skin after an exposure period of 4 hours or less; therefore, the test substance was not considered to be considered corrosive under the test guidelines. However, according to CLP regulation (EC 1272/2008), it is considered to be Category 1C (corrosive) (Klimisch 2, reliable with restrictions).

- *Surrogate: 44PD (CAS #101-96-2):* In a GLP-compliant skin irritation study (no guideline followed), six New Zealand white rabbits (sex not reported) were administered neat 44PD under occlusive conditions on shaved and shaved + abraded skin for 24 hours under occlusive conditions. Skin was observed through 21 days. Edema and erythema scores of 4/4 and 4/4 were assigned, with effects seen including scar tissue, hardening and sloughing of the skin, and formation of scabs. Based on these effects, it is considered to be corrosive (Klimisch 2, reliable with restrictions).

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *H*
CCPD was assigned a score of High for eye irritation/corrosivity based on ocular irritation effects seen in rabbits that are fully reversed within 21 days. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when classified as GHS Category 2A (irritating) (CPA 2018b). The confidence in the score is low as it is based on reliable data for a weak surrogate.

- 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 2021b
  - *Surrogate: 44PD (CAS #101-96-2):* In a GLP-compliant study (no guideline followed), the eyes of two New Zealand white rabbits (sex not reported) were instilled with neat 44PD (96.09% purity). No rinsing was reported, and eyes were observed, 24, 48, 72 hour, 7 days, 10 days, 14 days, and 17 days. Eye irritation effects were observed in the cornea, iris, and conjunctivae on the first three days after exposure, with all effects subsiding by day 14. Individual scores for sub-endpoints were not reported for every animal. The overall irritation score for animal #1 and #2 was 28/110 and 16.3/110, respectively (Klimisch 2, reliable with restrictions). ECHA dossier authors classified the test compound to GHS Category 2A based on the severity and reversibility of the effects observed in this study.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): *vH*
CCPD was assigned a score of Very High for acute aquatic toxicity based on the most conservative L/EC_{50} values of 0.13-0.939 mg/L for the surrogate 44PD, which are consistent with the predicted values of 0.21-0.54 mg/L for the target compound. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when L/EC_{50} values are <1 mg/L (CPA 2018b). The confidence in the score is low as it is based on reliable experimental data for a weak surrogate and modeled 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.
- U.S. EPA 2017b
  - CCPD belongs to the neutral organics ECOSAR chemical class. The most conservative predicted acute E/LC_{50} values are 0.27 mg/L in fish (96h), 0.21 mg/L in daphnia (48h), and 0.54 mg/L in green algae (96h) (Appendix G).
- ECHA 2021b
  - *Surrogate: 44PD (CAS #101-96-2):* 96-hour LC_{50} (*Lepomis macrochirus*) = 0.18 mg/L (GLP-compliant, Guideline method of acute toxicity tests with fish, macroinvertebrates, and amphibians) (Klimisch 2, reliable with restrictions)

- *Surrogate: 44PD (CAS #101-96-2):* 96-hour LC_{50} (*Oncorhynchus mykiss*) = 0.13 mg/L (GLP-compliant, Guideline method of acute toxicity tests with fish, macroinvertebrates, and amphibians) (Klimisch 2, reliable with restrictions)
- *Surrogate: 44PD (CAS #101-96-2):* 96-hour LC_{50} (*Pimephales promelas*) = 0.13 mg/L (GLP-compliant, Guideline method of acute toxicity tests with fish, macroinvertebrates, and amphibians) (Klimisch 2, reliable with restrictions)
- *Surrogate: 44PD (CAS #101-96-2):* 96-hour LC_{50} (*Oryzias latipes*) = 0.368 mg/L (GLP-compliant, Nr 1121002 EPA Japan) (Klimisch 1, reliable without restriction)
- *Surrogate: 44PD (CAS #101-96-2):* 48-hour mobility EC_{50} (*Daphnia magna*) = 0.54 mg/L (GLP-compliant, OECD Guideline 202) (Klimisch 1, reliable without restriction)
- *Surrogate: 44PD (CAS #101-96-2):* 48-hour mortality LC_{50} (*D. magna*) = 1.4 mg/L (GLP-compliant, Guideline method of acute toxicity tests with fish, macroinvertebrates, and amphibians) (Klimisch 2, reliable with restriction)
- *Surrogate: 44PD (CAS #101-96-2):* 72-hour growth rate EC_{50} (*Pseudokirchneriella subcapitata*) = 0.939 mg/L (GLP-compliant, Nr 1121002 EPA Japan) (Klimisch 1, reliable without restriction)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *vH*
CCPD was assigned a score of Very High for chronic aquatic toxicity based on modeled chronic aquatic toxicity values of 0.04-0.05 mg/L for fish and daphnia and a measured chronic toxicity value of 0.096 mg/L in algae for the surrogate 44PD. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when chronic aquatic toxicity data are ≤0.1 mg/L (CPA 2018b). The confidence in the score is low as it is primarily based 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.
- U.S. EPA 2017b
  - CCPD belongs to the neutral organics ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 0.04 mg/L in fish, 0.05 mg/L in daphnia, and 0.27 mg/L in green algae (Appendix G).
- ECHA 2021b
  - *Surrogate: 44PD (CAS #101-96-2):* 72-hour growth rate NOEC (*P. subcapitata*) = 0.096 mg/L (GLP-compliant, Nr 1121002 EPA Japan) (Klimisch 1, reliable without restriction)

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *H*
CCPD was assigned a score of High for persistence based on biodegradation predicted to take 75 days in the main compartment of soil. This is supported by the lack of biodegradation observed with the surrogate 77PPD. GreenScreen® criteria classify chemicals as a High hazard for persistence when the half-life in soil is >60 to 180 days (CPA 2018b). The confidence in the score is low as it is based 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.
- U.S. EPA 2017a
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that CCPD is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 15.1% will partition

to water with a half-life of 37.5 days, 0.815% will partition to sediment with a half-life of 337.5 days, and 84.1% will partition to soil with a half-life of 75 days (Appendix F).

- ECHA 2021a
  - *Surrogate: 77PPD (CAS #3081-14-9):* 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).
  - *Surrogate: 77PPD (CAS #3081-14-9):* 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: 77PPD (CAS #3081-14-9):* 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.
  - *Surrogate: 77PPD (CAS #3081-14-9):* The photolysis screening test of 77PPD in water shows a half-life of 2 hours with radiation, and of 4 hours in the dark.
  - *Surrogate: 77PPD (CAS #3081-14-9):* The calculated half-life for indirect hydrolysis in air is 3.7 hours.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *H*
CCPD was assigned a score of High for bioaccumulation based on a modeled BAF of 1,059. The log K_{ow} of 5.24 (estimated) corresponds to a Very High score. However, the modeled BAF takes precedence over the modeled log K_{ow}, as it takes metabolism into consideration. GreenScreen® criteria classify chemicals as a High hazard for bioaccumulation when BCF or BAF values are between 1,000 and 5,000 (CPA 2018b). The confidence in the score is low as it is based on modeled data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* EC – CEPA DSL - Bioaccumulative
- U.S. EPA 2017a
  - BCFBAF predicts a BAF of 1,059 using the Arnot-Gobas model for the upper trophic level, based on a modeled log K_{ow} of 5.24, taking metabolism into consideration (Appendix F).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
CCPD was assigned a score of Low for reactivity based on the absence of functional groups associated with explosive or self-reactive properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when the chemical does not warrant GHS classification as explosive or self-reactive and the chemical is not present on authoritative or screening lists (CPA 2018b). The confidence in the score is low based on the lack of experimental 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.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of CCPD. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, CCPD is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix H).
  - Based on the structure of its components or moieties, CCPD 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.

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

CCPD was assigned a score of Low for flammability based on a measured flash point of 178°C for the surrogate 77PPD, and 132-148°C for the surrogate 44PD which exceeds the criteria for GHS classification based on flash point > 93°C. Both surrogates are liquids and the flash points are sufficient to rule out flammability. 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 low as the target compound is predicted to be a solid, while both surrogates are liquid and non-flammable.

- *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021b
  - *Surrogate: 44PD (CAS #101-96-2):* Two experimental studies reported flash points of 132°C and 137-148°C for the test substance.
- ECHA 2021a
  - *Surrogate: 77PPD (CAS #3081-14-9)*: The flash point of 77PPD was 178°C in a closed cup method (GLP-compliant, EU Method A.9) (Klimisch 1, reliable without restriction).

Use of New Approach Methodologies (NAMs)[10] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for endocrine activity, respiratory sensitization, aquatic toxicity, persistence and bioaccumulation, and *in vitro* testing for genotoxicity. 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 4, Type I (input data) uncertainties in CCPD's NAMs dataset include the lack of sufficient data on endocrine activity, respiratory sensitization, aquatic toxicity, persistence, and bioaccumulation, along with a lack of validated test methods for respiratory sensitization. CCPD's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays in mimicking *in vivo* metabolic systems, the uncertain *in vivo* relevance of *in silico* modeling of endocrine receptor binding, the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization, and the lack of guidance from the ECHA framework to subclassify respiratory sensitizers to Category 1A and 1B. Some of CCPD's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Endocrine activity:** No experimental data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Bioaccumulation**: No experimental data are available for hazard classification. **Persistence**: No experimental data are available for hazard classification.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in

[10] 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).

	non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[11]. 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).[12] 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[13]. **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	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay, *in vitro* gene mutation assay, *in vitro* chromosome aberration 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	

[11] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[12] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[13] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

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	Y	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
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 CCPD (CAS #4175-38-6)

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	CCPD	4175-38-6	*L*	*L*	*L*	*M*	DG	*H*		*H*	*L*	DG	*H*	*M*	*vH*	*H*	*vH*	*vH*	*H*	*H*	*L*	*L*

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
CCPD	1

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
CCPD	1

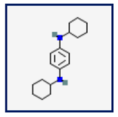
After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

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

APPENDIX C: Pharos Output for CCPD (CAS #4175-38-6)

Pharos | Search... | Comparisons | Common Products | Discussions | Account



4175-38-6
1,4-Benzenediamine, N,N'-dicyclohexyl-
ALSO CALLED N,N'-Dicyclohexyl-4-phenylenediamine, N,N'-Dicyclohexyl-p-phenylenediamine, UOP 26
View all synonyms (3)

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-UNK	-	-	-	-	-	pC	-	-	-	-	pC	-	pC	-	pC	-	-	-	vH	-	-	-	-	-	-	

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)	
Skin Sensitization	pC	NoGS	DK-EPA - Danish Advisory List	Skin Sens. 1 - May cause an allergic skin reaction (modeled)	
Skin Irritation/Corrosivity	pC	NoGS	DK-EPA - Danish Advisory List	Skin Irrit. 2 - Causes skin irritation (modeled)	

Acute Aquatic Toxicity	pC	NoGS	DK-EPA - Danish Advisory List	Aquatic Acute1 - Very toxic to aquatic life (modeled)	+1
	pC	NoGS	DK-EPA - Danish Advisory List	Aquatic Chronic1 - Very toxic to aquatic life with long lasting effects (modeled)	
Bioaccumulation	vH	LT-UNK	EC - CEPA DSL	Bioaccumulative	

Discussions

No discussions have been posted yet.

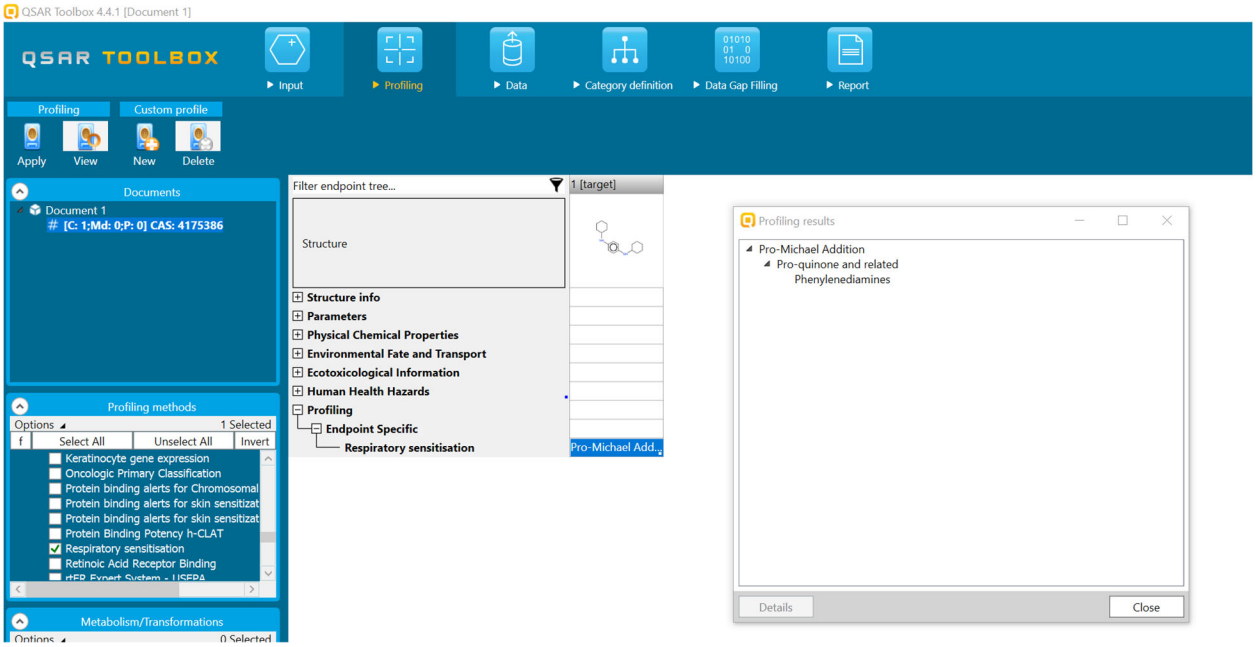
Ask a question about this chemical in the forums >

APPENDIX D: Danish (Q)SAR Database Endocrine Activity Results for CCPD (CAS #4175-38-6)

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		POS_OUT	POS_OUT	INC_OUT	POS_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		POS_OUT	POS_OUT	POS_OUT	POS_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_OUT	NEG_OUT	NEG_IN	NEG_OUT
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	NEG_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	POS_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	POS_OUT	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			43578.36	509.3906	10.15245
- µM			159955.8	1869.735	37.26491
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			8815.99	5.303113	167.9851
- µM			32359.38	19.46525	616.5949
- Positive for IC_{50} ≤ 10 µM					

APPENDIX E: OECD Toolbox Respiratory Sensitization Results for CCPD (CAS #4175-38-6)



APPENDIX F: EPI Suite™ Modeling Results for CCPD (CAS #4175-38-6)

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

CAS Number: 4175-38-6
SMILES : N(c(ccc(NC(CCCC1)C1)c2)c2)C(CCCC3)C3
CHEM : 1,4-Benzenediamine, N,N -dicyclohexyl-
MOL FOR: C18 H28 N2
MOL WT : 272.44
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
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) = 5.24

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 379.45 (Adapted Stein & Brown method)
Melting Pt (deg C): 131.43 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 2.24E-006 (Modified Grain method)
VP (Pa, 25 deg C) : 0.000299 (Modified Grain method)
Subcooled liquid VP: 2.61E-005 mm Hg (25 deg C, Mod-Grain method)
: 0.00348 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 0.5896
log Kow used: 5.24 (estimated)
no-melting pt equation used

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 4.4631 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.07E-008 atm-m3/mole (1.09E-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: 1.362E-006 atm-m3/mole (1.380E-001 Pa-m3/mole)

VP: 2.24E-006 mm Hg (source: MPBPVP)
WS: 0.59 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 5.24 (KowWin est)
Log Kaw used: -6.359 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 11.599
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.1503
Biowin2 (Non-Linear Model) : 0.0092
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.3272 (weeks-months)
Biowin4 (Primary Survey Model) : 3.2379 (weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.0286
Biowin6 (MITI Non-Linear Model): 0.0136
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -1.2225
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): 0.00348 Pa (2.61E-005 mm Hg)
Log Koa (Koawin est): 11.599
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.000862
Octanol/air (Koa) model: 0.0975
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.0302
Mackay model : 0.0645
Octanol/air (Koa) model: 0.886

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 138.6095 E-12 cm3/molecule-sec
Half-Life = 0.077 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 0.926 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.0474 (Junge-Pankow, Mackay avg)
0.886 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):

Koc : 981.6 L/kg (MCI method)
Log Koc: 2.992 (MCI method)
Koc : 1162 L/kg (Kow method)
Log Koc: 3.065 (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 = 3.126 (BCF = 1337 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.4232 days (HL = 2.65 days)
Log BCF Arnot-Gobas method (upper trophic) = 2.999 (BCF = 998.3)
Log BAF Arnot-Gobas method (upper trophic) = 3.025 (BAF = 1059)
log Kow used: 5.24 (estimated)

Volatilization from Water:
Henry LC: 1.07E-008 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 9.032E+004 hours (3763 days)
Half-Life from Model Lake : 9.854E+005 hours (4.106E+004 days)

Removal In Wastewater Treatment:
Total removal: 83.98 percent
Total biodegradation: 0.72 percent
Total sludge adsorption: 83.26 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	**0.041**	**1.85**	**1000**
Water	**15.1**	**900**	**1000**
Soil	**84.1**	**1.8e+003**	**1000**
Sediment	**0.815**	**8.1e+003**	**0**

Persistence Time: 1.34e+003 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.041	1.85	1000
Water	15.1	900	1000
water	(14.9)		
biota	(0.13)		
suspended sediment	(0.022)		
Soil	84.1	1.8e+003	1000
Sediment	0.815	8.1e+003	0

Persistence Time: 1.34e+003 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0285	1.85	1000
Water	8.3	900	1000
water	(7.44)		
biota	(0.0646)		
suspended sediment	(0.795)		
Soil	60.1	1.8e+003	1000
Sediment	31.6	8.1e+003	0
Persistence Time:	1.92e+003 hr		

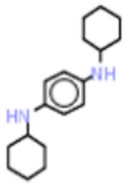
APPENDIX G: ECOSAR Modeling Results for CCPD (CAS #4175-38-6)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
4175386	1,4-Benzenediamine, N,N -dicyclohexyl-	N(c(ccc(NC(CCCC1)C1)c2)c2)C(CCCC3)C3

Structure



Details	
Mol Wt	272.44
Selected LogKow	5.24
Selected Water Solubility (mg/L)	0.59
Selected Melting Point (°C)	
Estimated LogKow	5.24
Estimated Water Solubility (mg/L)	0.59
Measured LogKow	
Measured Water Solubility (mg/L)	
Measured Melting Point (°C)	

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	0.27	5	
Daphnid	48h	LC50	0.21	5	
Green Algae	96h	EC50	0.54	6.4	
Fish		ChV	0.04	8	
Daphnid		ChV	0.05	8	
Green Algae		ChV	0.27	8	

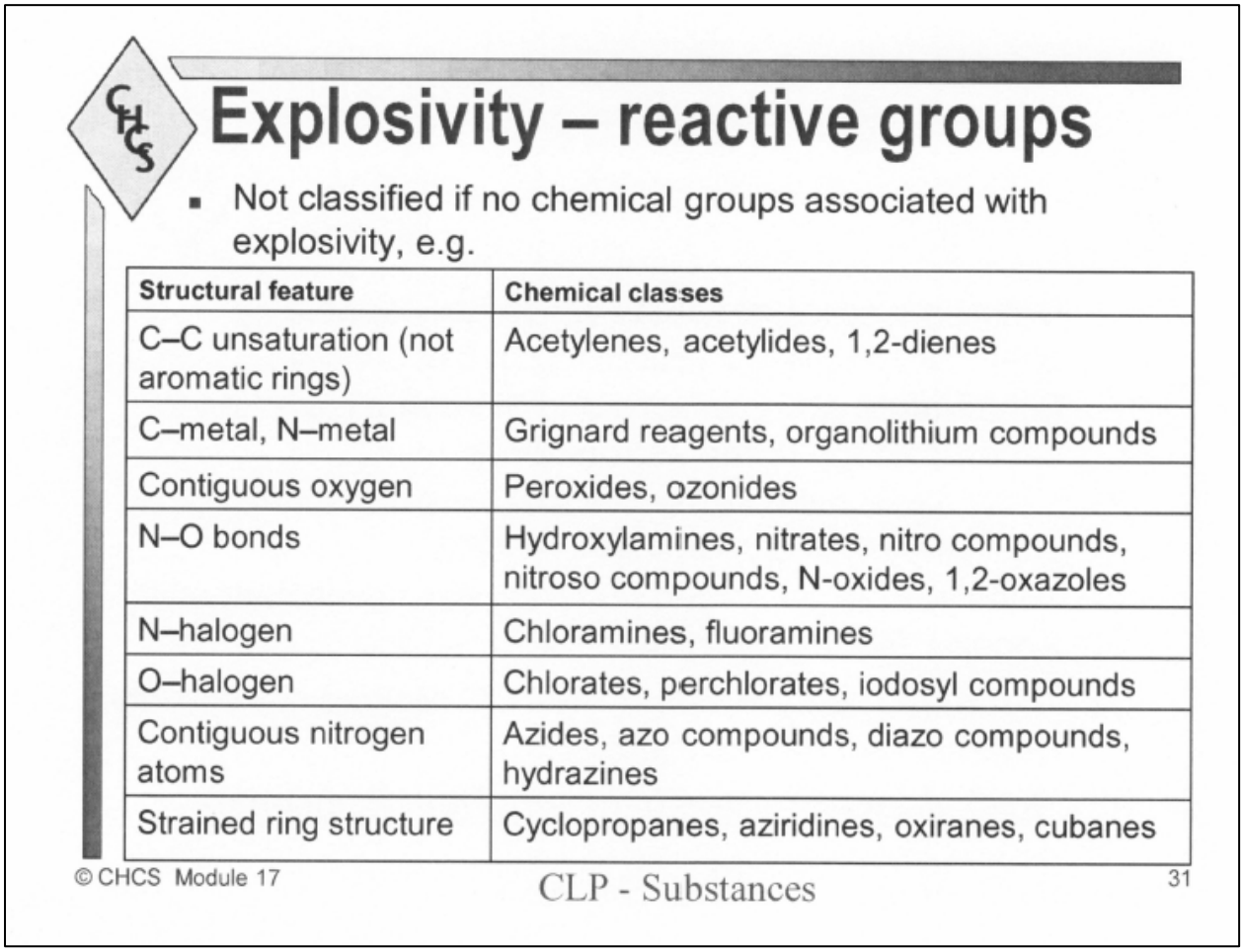
1 / 2

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish (SW)	96h	LC50	0.35	5	
Mysid	96h	LC50	0.03	5	
Fish (SW)		ChV	0.28	8	
Mysid (SW)		ChV	0	8	
Earthworm	14d	LC50	218.37	6	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

APPENDIX H: 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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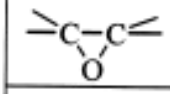
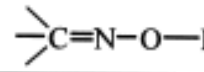
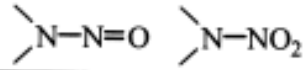
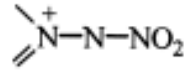
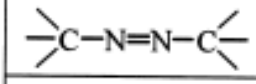
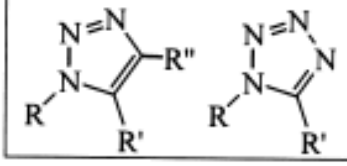
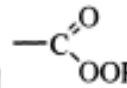
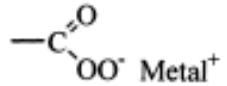
Explosivity – Full List

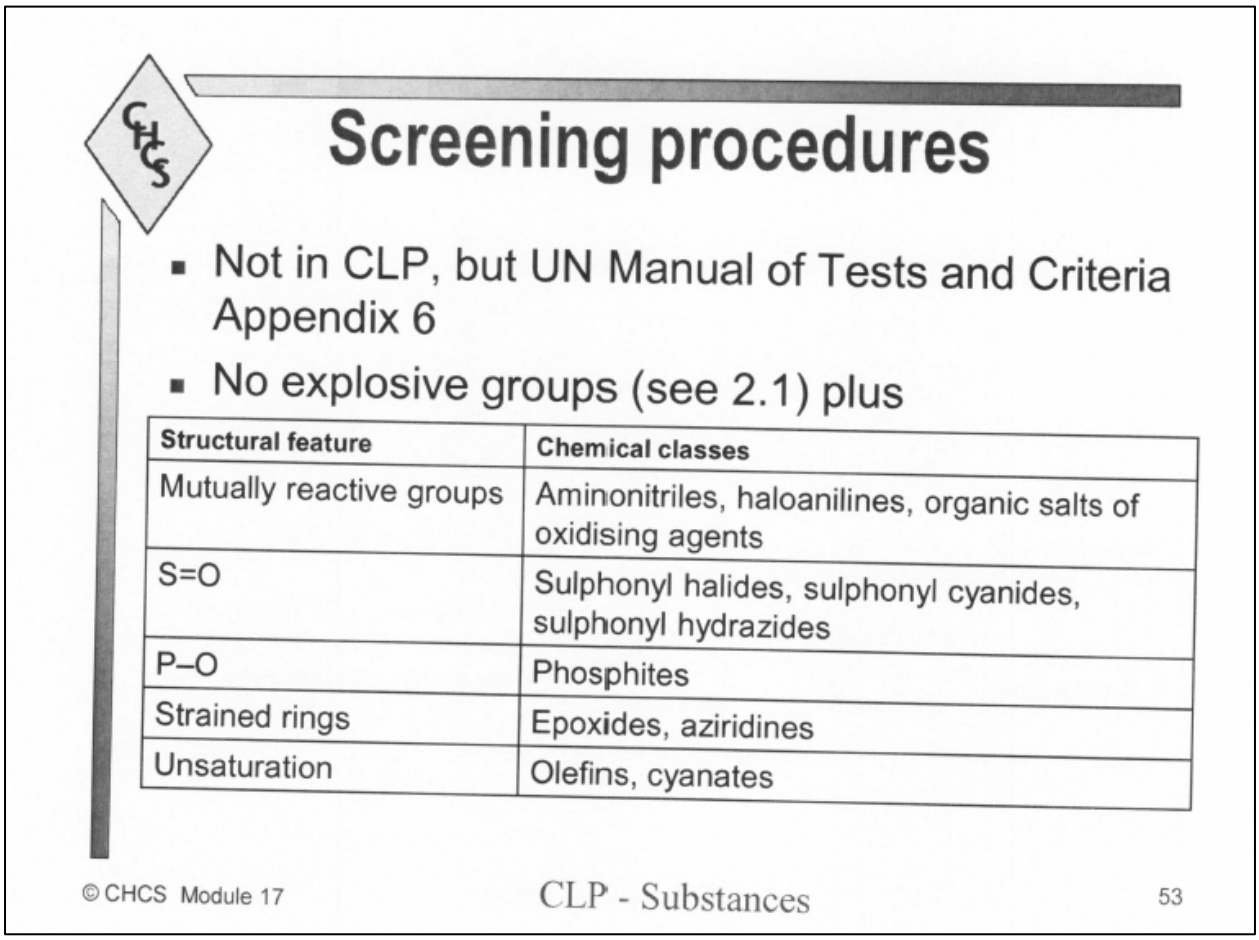
Table R.7.1-28 Chemical groups associated with explosive properties

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 I: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for CCPD. There has been one round of update which did not change the Benchmark score.

Table 5: Change in GreenScreen® Benchmark™ for CCPD

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
October 19, 2021	BM-1	v. 1.4	New assessment
November 5, 2021	BM-1	v. 1.4	Minor revisions in response to Washing Ecology's comments

Licensed GreenScreen® Profilers

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