

N-1,3-DIMETHYL BUTYL-N'-PHENYL QUINONE DIAMINE (6QDI)
(CAS #52870-46-9)
GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 8, 2021

ToxServices Review Date: November 8, 2026¹



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.

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GreenScreen® Executive Summary for N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) functions as an anti-degradant and processing aid. It is a dark oily liquid under standard temperature and pressure. It is non-reactive, non-flammable, non-volatile, and insoluble to slightly soluble in water.

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) 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
 - Very High persistence-P + High bioaccumulation-B + Very High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA)
 - Very High P + High B + High Group I Human Health Hazard (reproductive toxicity-R)
 - Very High P + High B + High Group II* Human Health Hazard (skin sensitization-SnS*)
- Benchmark 1c
 - Very High P + Very High Ecotoxicity (AA and CA)
 - Very High P + High Group I Human Health Hazard (R)
 - Very High P + High Group II* Human Health Hazard (SnS*)
- Benchmark 1e
 - High Group 1 Human Health Hazard (R)

Data gaps (DG) exist for repeated dose neurotoxicity-Nr* and respiratory sensitization-SnR*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) meets requirements for a GreenScreen Benchmark™ Score of 1 despite the hazard data gaps. In a worst-case scenario, if N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) were assigned a High score for the data gaps Nr* or SnR*, it would still be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* genotoxicity, cell transformation, and endocrine activity testing, *in silico* modeling for endocrine activity, respiratory sensitization, persistence, and bioaccumulation, and a modified Sturm biodegradation test. 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 N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI)'s NAMs dataset include lack of experimental data for respiratory sensitization along with a lack of validated test method for respiratory sensitization. N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI)'s Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of OECD Toolbox in identifying structural alerts without defining the applicability domain, the uncertain relevance of the EDSP Tox 21 screening assays and *in silico* modeling of endocrine receptor binding due to lack of consideration of toxicokinetic factors including metabolism, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI)'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 N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI)

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	H	M	M	M	M	M	M	DG	H	DG	L	H	vH	vH	vH	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-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)

Method Version: GreenScreen® Version 1.4

Assessment Type²: Certified

Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.4) Prepared By:

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Date: October 14, 2021, November 2, 2021

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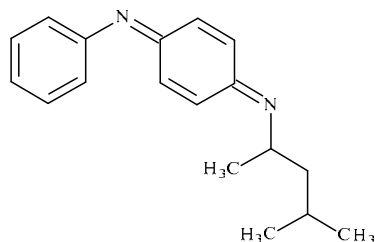
Date: October 15, 2021, November 8, 2021

ToxServices Review Date: November 8, 2026³

Chemical Name: N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI)

CAS Number: 52870-46-9

Chemical Structure(s):



Also called:

EC 429-640-2; Benzenamine, N-(4-((1,3-dimethylbutyl)imino)-2,5-cyclohexadien-1-ylidene)-; N-(1,3-Dimethylbutyl)-N'-(phenyl)-1,4-benzoquinonediimine; Benzenamine, N-[4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylidene]-; Benzenamine, N-4-(1,3-dimethylbutyl)imino-2,5-cyclohexadien-1-ylidene-; EC 429-640-2; N-(1,3-Dimethylbutyl)-N'-phenyl-p-benzoquinone diamine; [4-(1,3-dimethylbutylimino)-cyclohexa-2,5-dienylidene]-phenyl-amine; 4-N-(4-methylpentan-2-yl)-1-N-phenylcyclohexa-2,5-diene-1,4-diimine (ChemIDplus 2021, PubChem 2021)

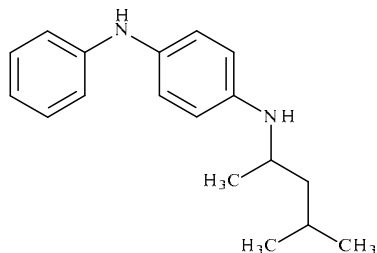
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):

ToxServices identified limited data for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI). It is the oxidized form of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8) and is expected to form readily in the presence of oxygen under hydrolytic conditions (ECHA 2021a). Therefore, ToxServices used data for N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) to address data gaps for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI). For the bioaccumulation endpoint, ToxServices used N-(1-methylheptyl)-N'-phenylbenzene-1,4-diamine (CAS

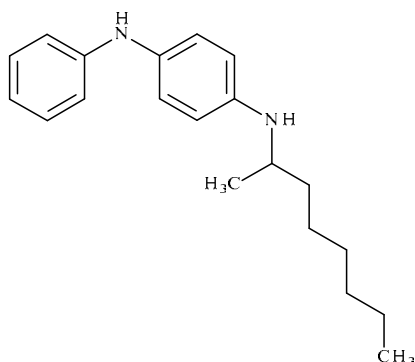
² GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).

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.

#15233-47-3) as a surrogate, which is a read-across chemical in the REACH registration dossier for the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD).



Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)



Surrogate: N-(1-Methylheptyl)-N'-phenylbenzene-1,4-diamine (CAS #15233-47-3)

Identify Applications/Functional Uses (Flexsys 2007):

1. Anti-degradant.
2. Processing aid.

Known Impurities⁴:

No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI)^{5,6}

^{7,8}: N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) 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
 - Very High persistence-P + High bioaccumulation-B + Very High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA)
 - Very High P + High B + High Group I Human Health Hazard (reproductive toxicity-R)
 - Very High P + High B + High Group II* Human Health Hazard (skin sensitization-SnS*)

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

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.

- Benchmark 1c
 - Very High P + Very High Ecotoxicity (AA and CA)
 - Very High P + High Group I Human Health Hazard (R)
 - Very High P + High Group II* Human Health Hazard (SnS*)
- Benchmark 1e
 - High Group 1 Human Health Hazard (reproductive toxicity-R)

Data gaps (DG) exist for repeated dose neurotoxicity-Nr* and respiratory sensitization-SnR*. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) meets requirements for a GreenScreen Benchmark™ Score of 1 despite the hazard data gaps. In a worst-case scenario, if N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) were assigned a High score for the data gaps Nr* or SnR*, it would still be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI)

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) readily hydrolyzes at neutral pH and 25°C, as demonstrated in an OECD Guideline 111 test (ECHA 2021a,b). The hydrolysis products were identified as 4-hydroxy-diphenylamine (CAS #122-37-2), p-benzoquinone (CAS #106-54-1), p-hydroquinone (CAS #123-31-9), and aniline (CAS #62-53-3). 4-Hydroxy-diphenylamine and p-benzoquinone are not listed as LT-1 chemicals in the Pharos database, whereas p-hydroquinone and aniline are listed as LT-1 chemicals. However, both aniline (ECB 2004) and hydroquinone (UNEP 2002) are readily biodegradable. Therefore, the Benchmark Score for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) is not modified by the environmental transformation products.

Table 1: Environmental Transformation Product Summary						
Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score^{9,10}
End	Hydrolysis	4-Hydroxy-diphenylamine	122-37-2	Yes	Yes	LT-UNK
End	Hydrolysis	p-Benzoquinone	106-51-4	Yes	Yes	LT-P1
End	Hydrolysis	p-Hydroquinone	123-31-9	Yes	No	LT-1
End	Hydrolysis	Aniline	62-53-3	Yes	No	LT-1

Introduction

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) is used as an anti-degradant and processing aid (Flexsys 2007). It is the oxidized form of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) which is used as an antioxidant, antiozonant, and polymer stabilizer in butadiene rubber, nitrile-butadiene rubber, styrene-butadiene rubber, and synthetic isoprene rubber (HSDB 2002).

ToxServices assessed N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2021a). It can be accessed at: <http://www2.epa.gov/saferchoice/safer-ingredients>. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) 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),¹¹ 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 N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) can be found in Appendix C.

- N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) is not listed on the U.S. DOT list.

⁹ The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.

¹⁰ A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

¹¹ DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

- N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) is not on any 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

A harmonized European Union (EU) Globally Harmonized System of Classification and Labelling of Chemicals (GHS) classification is available for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) (ECHA 2021c); it is classified as a GHS Category 2A eye irritant (H319), a GHS Category 1 acute aquatic toxicant (H400), and a GHS Category 1 chronic aquatic toxicant (H410), as indicated in Table 2. General personal protective equipment (PPE) recommendations are presented in Table 3, below. No occupational exposure limits (OELs) were identified.

Table 2: GHS H Statements for N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9) (ECHA 2021c)	
H Statement	H Statement Details
H319	Causes serious eye irritation
H400	Very toxic to aquatic life
H410	Very toxic to aquatic life with long lasting effects

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)			
Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Chemical goggles/face shield, protective clothing, gloves, respiratory protection (when engineering controls are inadequate)	Flexsys 2007	None identified	

Physicochemical Properties of N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI)

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) is a dark, oily liquid under standard temperature and pressure. It has a low vapor pressure (0.000004-0.0000075 mm Hg) indicating it exists mostly in the liquid phase. It is insoluble to slightly soluble in water, but is more soluble in octanol (log K_{ow} = 4.2).

Table 4: Physical and Chemical Properties of N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)		
Property	Value	Reference
Molecular formula	C18-H22-N2	ChemIDplus 2021
SMILES Notation	<chem>CC(C)CC(C)N=C1C=CC(=Nc2ccccc2)C=C1</chem>	ChemIDplus 2021
	<chem>CC(C)CC(C)N=C1C=CC(=NC2=CC=C(C=C2)C=C1</chem>	PubChem 2021
Molecular weight	266.3858 g/mol	ChemIDplus 2021
Physical state	Liquid	ECHA 2021b
Appearance	Dark, oily	Flexsys 2007
Melting point	-10°C	ECHA 2021b
Boiling point	> 300°C	ECHA 2021b
Vapor pressure	0.001 Pa (0.0000075 mm Hg) at 25°C	ECHA 2021b

Table 4: Physical and Chemical Properties of N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)		
Property	Value	Reference
	0.000529 Pa (0.000004 mm Hg) at 25°C	Flexsys 2007
Water solubility	15.4 mg/L at 20°C Insoluble	ECHA 2021b Flexsys 2007
Dissociation constant	Not identified	
Density/specific gravity	Relative density = 1 at 20°C	ECHA 2021b
Partition coefficient	Log K _{ow} = 4.2 at 25°C	ECHA 2021b

Toxicokinetics

- **Absorption**
 - No data are available for the *in vivo* absorption of N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) or the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD). Based on the toxicity identified following oral dosing with the surrogate, this chemical is presumed to be absorbed following oral dosing (UNEP 2005). Due to the lower oral LD₅₀ obtained for rats dosed with the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) in olive oil compared to dosing without a vehicle, absorption from the gastrointestinal tract may be greater when present in a lipid/fat-rich medium.
- **Distribution**
 - No data are available for the *in vivo* distribution of N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) or the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD).
- **Metabolism**
 - When placed in gastric juice (origin not specified), the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13) had a hydrolysis half-life of 36.9 hours. The major hydrolysis product was identified as aniline, with lesser amounts of benzoquinoneimine-N-phenyl (CAS #N/A) and N-1,3 dimethyl-butylamine p-phenol (CAS #N/A), and possibly quinone (CAS #106-51-4) and 2-amino-4-methylpentane (CAS #108-09-8) (Klimisch Score 2, reliable with restrictions) (ECHA 2021a). No additional metabolism studies were identified.
- **Excretion**
 - No data are available for the excretion of N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) or the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Low for carcinogenicity based on the lack of carcinogenicity identified in two chronic feeding studies in rats and negative results for cell transformation for the surrogate. 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 high as it is based on reliable measured data on a strong 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.
- UNEP 2005, ECHA 2021a
 - *Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):*
A non-GLP-compliant chronic feeding study conducted in a manner similar to OECD Guideline 451 was performed with Sprague-Dawley rats (70/sex/group) provided diets containing N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, 100% active ingredient) at 0, 50, 250, or 1,500 ppm (providing doses of 2.6, 13.5, and 84.8 mg/kg/day for males, and 3.2, 16.5, and 109.5 mg/kg/day for females, respectively) for up to two years. After 12 months, 20 rats/sex/group were sacrificed, and the remaining animals were sacrificed after 24 months. A slight, non-statistically significant increase in the incidence of thyroid follicular cell carcinoma was identified in male rats (the control, low, mid, high dose group incidences were 0/70, 0/69, 2/70, and 3/69, respectively). No such increase was identified in female rats. Reviews in the literature suggest that the increased incidence of this neoplasm may be due to increased liver activity and disruption of thyroid-pituitary signaling and may not be relevant for humans. Therefore, the authors concluded that N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) is not likely to be carcinogenic (Klimisch Score 2, reliable with restrictions).
 - *Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):*
A non-GLP-compliant feeding study was performed with Charles River (CD Outbred) rats (50/sex/group) provided diets containing N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, purity not specified) at 0, 100, 300, or 1,000 ppm (contributing doses of 8, 23, and 75 mg/kg/day, respectively) for 24 months. Treatment did not increase the tumor frequency or type of tumors relative to those identified in the control group (Klimisch Score 2, reliable with restrictions).
 - *Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):*
A GLP-compliant *in vitro* cell transformation assay was performed with BALB/3T3 cells exposed to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (purity not specified) at 0.61-1,000 µg/mL (range finding) and 0.165-0.99 µg/mL (cell transformation assay). Exposure to ≥ 0.488 µg/mL resulted in ≤ 32.3% relative survival. Treatment did not increase the frequency of transformed foci relative to the solvent control, whereas the positive control (methylcholanthrene) produced the expected increase in transformed foci (Klimisch Score 2, reliable with restrictions).

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Low for mutagenicity/genotoxicity based on negative mutagenicity data *in vitro* and negative clastogenicity data *in vivo* for the 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 high as it is based on reliable measured data on a strong 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
 - The REACH dossier for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) presents bacterial reverse mutation and mammalian cell chromosome aberration assays but no results and limited data are provided.

- UNEP 2005, ECHA 2021a
 - Note: Due to the high volume of studies provided in the dossiers, only the key *in vitro* studies are summarized and evaluated in this assessment.
 - *In vitro*: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A GLP-compliant, OECD Guideline 471/Japanese Guidelines for Screening Mutagenicity Testing Of Chemicals bacterial reverse mutation assay was performed with *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP2 uvr A exposed to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (99% purity) in dimethyl sulfoxide (DMSO) at ≤ 156 $\mu\text{g}/\text{plate}$ (*S. typhimurium*) or $\leq 5,000$ $\mu\text{g}/\text{plate}$ (*E. coli*) with and without exogenous metabolic activation (unspecified S9 mix). Treatment did not increase the mutation frequency in the presence or absence of metabolic activation, but was evaluated at up to cytotoxic concentrations or guideline concentration limits. The vehicle and positive (2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide, sodium azide, 9-aminoacridine, and 2-aminoanthracene) controls were reported as valid (Klimisch Score 1, reliable without restriction).
 - *In vitro*: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A GLP-compliant mammalian cell gene mutation assay was performed with Chinese hamster ovary (CHO) cells exposed to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, purity not specified) in DMSO at ≤ 5 $\mu\text{g}/\text{mL}$ without and ≤ 24 $\mu\text{g}/\text{mL}$ with exogenous metabolic activation (unspecified S9 mix). Treatment did not increase the mutation frequency in the presence or absence of metabolic activation when tested up to cytotoxic concentrations. The vehicle and positive (ethylmethanesulphonate and benzo(a)pyrene) controls were reported as valid (Klimisch Score 1, reliable without restriction).
 - *In vitro*: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A GLP-compliant, OECD Guideline 473/Japanese Guidelines for Screening Mutagenicity Testing Of Chemicals mammalian chromosome aberration test was performed with Chinese hamster lung cells (CHL/IU) exposed to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (99% purity) in DMSO at ≤ 0.01 mg/mL without metabolic activation for continuous treatment and ≤ 0.0025 mg/mL without and ≤ 0.015 mg/mL with exogenous metabolic activation (unspecified S9 mix) for short-term treatment. Cytotoxicity was evidence at ≥ 0.02 mg/mL during the continuous exposure and at ≥ 0.005 mg/mL without and ≥ 0.03 mg/mL with metabolic activation during the short-term exposure. Treatment increased chromosome aberration frequencies during the continuous exposure at ≥ 0.005 mg/mL at 24 hours and ≥ 0.01 mg/mL at 48 hours. Treatment did not increase the chromosome aberration frequency during the short-term exposures in the presence or absence of metabolic activation. The vehicle, untreated negative, and positive (mitomycin C and cyclophosphamide) controls were reported as valid (Klimisch Score 1, reliable without restriction).
 - *In vivo*: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A GLP-compliant chromosome aberration test was performed with Sprague-Dawley rats (5/sex/group) administered single gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, purity not specified) in corn oil at 1,000 mg/kg and sacrificed 6, 18, or 30 hours after dosing. Femoral bone marrow was isolated for the clastogenicity assessment. Treatment did not increase the frequency of chromosome aberrations. Toxicity was evident as clinical signs of toxicity and gross pathological changes, indicating absorption of the test material from the gastrointestinal

- tract. The vehicle and positive (cyclophosphamide) controls were reported as valid (Klimisch Score 1, reliable without restriction).
- o *In vivo: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A chromosome aberration assay was performed with male Swiss mice (5/group) administered two intraperitoneal injections of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (purity not specified) in 1% gum acacia at 0, 100, or 200 mg/kg/day within 24 hours of each other. The animals were sacrificed 24 hours after the second injection. Treatment did not increase the frequency of chromosome aberrations. The vehicle and positive control (cyclophosphamide) were reported as valid (Klimisch Score 2, reliable with restrictions).
 - o *In vivo: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A GLP-compliant micronucleus assay was performed with CD-1 mice (5/sex/group) administered single intraperitoneal injections of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Flexzone 7F and 7L, purity not specified) in corn oil at 0 or 1,000 mg/kg and sacrificed 30, 48, or 72 hours. Treatment did not increase the frequency of micronuclei in erythrocytes, but toxicity was evident based on clinical signs of toxicity. The vehicle and positive (triethylenemelamine) controls were reported as valid (Klimisch Score 2, reliable with restrictions).¹²
 - o *In vivo: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A micronucleus test was performed with male Swiss mice (5/group) administered two intraperitoneal injections of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (purity not specified) in 1% gum acacia at 0, 100, 150, or 200 mg/kg/day within 24 hours of each other. The animals were sacrificed 24 hours after the second injection and bone marrow cells were isolated for the micronuclei assessment. Treatment did not increase the frequency of micronuclei. The vehicle and positive (cyclophosphamide) controls were reported as valid (Klimisch Score 2, reliable with restrictions).
- In summary, the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was not mutagenic in bacterial or mammalian cells. While it was clastogenic in CHL/IU cells during the continuous exposure in the absence of metabolic activation, N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine treatment did not increase the frequency of chromosome aberrations or micronuclei in *in vivo* rodent studies. Therefore, ToxServices concludes that N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) is not likely to be genotoxic *in vivo*.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of High for reproductive toxicity based on ToxServices classifying the surrogate as a GHS Category 1B reproductive toxicant. GreenScreen® criteria classify chemicals as a High hazard for reproductive toxicity when they are classified as GHS Category 1B reproductive toxicants (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on a strong surrogate.

- Authoritative and Screening Lists
 - o *Authoritative:* Not present on any authoritative lists for this endpoint.
 - o *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
 - o *Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A GLP-compliant, OECD Guideline 443 extended one-generation reproductive toxicity

¹² Note: This study is presented in the SIDS dossier with a Klimisch Score 1 (reliable without restriction). Whenever there is a discrepancy between reliability scores, ToxServices presents the lowest score.

- study was performed with Sprague-Dawley rats (25-30/sex/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (95.7% purity) in corn oil at 7, 20, or 60 mg/kg/day. F0 males were dosed for 70 consecutive days prior to mating and through mating for a minimum of 10 weeks. F0 females were dosed for 70 consecutive days prior to mating, during mating, gestation, and lactation, and until weaning of the F1 pups. The parental animals were evaluated for clinical signs of toxicity, estrous cyclicity, sperm parameters (numbers, production rate, motility, progressive motility, and morphology), gross pathology, histopathology, and reproductive performance. Treatment did not adversely affect sperm parameters or male reproductive performance. Two and five females in the mid and high dose groups, respectively, were found dead or euthanized *in extremis* on gestation day 21 through lactation day 2. The authors attributed to deaths and moribund condition to prolonged labor and/or dystocia (difficult birth). Therefore, the authors identified a female reproductive toxicity NOAEL of 7 mg/kg/day based on the dystocia identified at 20 and 60 mg/kg/day (Klimisch Score 1, reliable without restriction).
- o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A GLP-compliant reproduction / developmental toxicity screening test conducted in a manner similar to OECD Guideline 421 was used as the dose range-finding study for the OECD Guideline 443 study discussed above. Sprague-Dawley rats (15/sex/group) were administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (96.9% purity) in corn oil at 0, 50, 75, or 100 mg/kg/day. Males were dosed for at least 14 days prior to mating and through mating for 28 days. Females were dosed for at least 14 days prior to mating and through mating, gestation, and lactation. Over the course of the study, one female each in the low and mid dose groups were found dead and one and three females each in the low and high dose groups were euthanized *in extremis*. No treatment-related effects were identified for body weight, food consumption, thyroid hormone levels [triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH)], or histopathological findings. Treatment did not adversely affect mating, fertility, or copulation/conception indices or the mean estrous cycle lengths, but mean gestation lengths in the treatment group were greater than the concurrent control group (statistical significance not provided). Dystocia was identified for one, one, and five females in the low, mid, and high dose groups, respectively, including for the three high dose females sacrificed *in extremis*. As this was a dose range-finding study, the authors did not identify a reproductive toxicity NOAEL (Klimisch Score 1, reliable with restrictions).
 - UNEP 2005, ECHA 2021a
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A GLP-compliant, OECD Guideline 421 reproduction/developmental toxicity screening test was performed with Crj: CD(SD) rats (12/sex/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (99.4% purity) in corn oil at 0, 6, 25, or 100 mg/kg/day. Males were dosed for 48 days, and females were dosed for 14 days prior to mating until lactation/postnatal day 3. Treatment did not affect body weight gain, and food consumption rates increased intermittently in high dose males and in females in all dose groups during lactation only. Treatment did not adversely affect the copulation or fertility index or estrus cyclicity, but the gestation length was statistically significantly greater in the high dose group (22.7 days) compared to the concurrent control group (22.2 days). The authors identified a reproductive toxicity NOAEL of 100 mg/kg/day based on the lack of adverse effects on fertility (Klimisch Score 1, reliable without restrictions).
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A non-GLP-compliant three-generation reproduction toxicity test was performed with

Charles River CD rats (8 males and 15 females per group per generation) provided diets containing N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13) at 0, 100, 300, or 1,000 ppm (contributing doses of 0, 8, 23, and 75 mg/kg/day, respectively). The F0 males and females were treated for 11 weeks prior to mating, and the exposure continued through mating, gestation, and lactation for two successive litters. The mating and fertility indices, incidence of parturition, mean number of live and dead pups at birth, and number of pups weaned were comparable between the control and treatment groups. The fertility indices for mid dose F1b males and F2a females were lower than controls but the authors attributed these findings to their poor health (decreased body weights and decreased survival). The authors concluded that treatment did not adversely affect fertility in this study and identified a reproductive toxicity NOAEL of 1,000 ppm (75 mg/kg/day) the highest dose tested (Klimisch Score 2, reliable with restrictions).

- In summary, while the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) did not adversely affect fertility, several studies identified increased gestation length and/or an increased incidence of dystocia with treatment. As multiple studies identified dystocia with treatment and due to the potential adverse impacts on the health of the mother and offspring, the REACH dossier authors classified N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) as a GHS Category 1B reproductive toxicant. ToxServices agrees with this classification for the surrogate and assigned the hazard score for this endpoint based on this classification.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Moderate for developmental toxicity based on decreased fetal body weights and/or increased post-implantation losses identified in rat and rabbit prenatal developmental toxicity tests of the surrogate, sometimes identified at maternally-toxic doses, and altered female pubertal development in rats exposed to the surrogate. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when limited or marginal evidence of developmental toxicity is available in animals (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on a strong 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.
- UNEP 2005, ECHA 2021a
 - *Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A GLP-compliant prenatal developmental toxicity test conducted in a manner similar to OECD Guideline 414 was performed with pregnant female Sprague-Dawley rats (25/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, 100% purity) in corn oil at 50, 100, or 250 mg/kg/day on gestation days 6-15. The animals were sacrificed on gestation day 20. Dams in the mid and high dose groups exhibited increased incidences of salivation, diarrhea, soft stool, green staining of the anogenital fur, and green fecal discoloration. Treatment did not adversely impact maternal body weights or body weight gains. High dose dams exhibited decreased food consumption during the first three days of treatment, but food consumption increased following the exposure period. Treatment did not adversely affect the number of viable fetuses, early and late resorptions, fetal sex ratio, fetal weights, or the types and incidences of fetal malformations or variations. The authors identified a maternal toxicity NOAEL of 50 mg/kg/day based on clinical signs of toxicity and a teratogenicity NOAEL of 250 mg/kg/day based on the lack of malformations induced at up to the highest dose tested.
 - The REACH dossier assigned this study a Klimisch Score of 1 (reliable without

restriction). In contrast, the SIDS dossier authors assigned it a Klimisch Score of 4 (not assignable).

- o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A non-GLP-compliant prenatal developmental toxicity test was performed with pregnant female New Zealand albino rabbits (17-23/group) administered oral doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, purity not specified) in gelatin capsules at 0, 10, or 30 mg/kg/day on gestation days 6-18. Treatment decreased body weights in all dose groups during the dosing period, with controls and high dose animals exhibiting decreased overall body weights. Mortality rates were 5/17 (29%), 3/17 (17%), and 6/23 (26%) for the control, low dose, and high dose groups, respectively. Two dams in the low and high dose groups had terminated pregnancies. The relative resorption rates were 31.4%, 30.5%, and 38.6% for the control, low dose, and high dose groups respectively, indicating an increased resorption rate for the high dose group (statistical significance not provided). The relative number of live offspring (per 100 implantation sites) in the control, low dose, and high dose groups were 68.8%, 48.3%, and 38.6%, respectively, indicating a dose-related decrease in fetal viability. One pup in a high dose litter exhibited spina bifida, but the authors concluded the incidence was too low to attribute this finding to the treatment. No other external, visceral, or skeletal malformations were identified with treatment. The authors identified a maternal toxicity and developmental toxicity NOAEL of 30 mg/kg/day. ToxServices disagrees with the selection of the developmental toxicity NOAEL based on the reduced fetal viability at both dose groups tested. Therefore, ToxServices identified a developmental toxicity LOAEL of 10 mg/kg/day for this study based on the decreased fetal viability at ≥ 10 mg/kg/day (Klimisch Score 2, reliable with restrictions).
- o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A GLP-compliant OECD Guideline 421 reproduction/developmental toxicity screening test was performed with Crj: CD(SD) rats (12/sex/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (99.4% purity) in corn oil at 0, 6, 25, or 100 mg/kg/day. Females were dosed for 14 days prior to mating until lactation/postnatal day 3. Treatment did not affect maternal body weight gain, but increased food consumption for females in all treatment groups during lactation. Treatment reduced the total number of pups born (control, low, mid, high dose: 184, 160, 149*, 131), total live pups born (183, 158, 148*, and 131), and number of live pups on postnatal day 4 (males: 81, 74, 74, and 72; females: 78, 80, 71, and 57) (* = $p < 0.05$). Pup body weights at birth and at postnatal day 4 increased in the mid and high dose groups, possibly due to the increased amount of nutrition delivered on an individual basis with the decreased litter sizes. Treatment did not increase the incidence of external malformations. The authors identified a maternal toxicity NOAEL of 6 mg/kg/day based on systemic toxicity (see the systemic toxicity section below for details) and a developmental toxicity NOAEL of 100 mg/kg/day based on the lack of teratogenicity. ToxServices identified a developmental toxicity NOAEL of 6 mg/kg/day based on statistically significantly reduced number of pups born and live pups on postnatal day 4 at ≥ 25 mg/kg/day (Klimisch Score 1, reliable without restriction).
- ECHA 2021a
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A GLP-compliant, OECD Guideline 414 prenatal developmental toxicity test was performed with pregnant female New Zealand White rabbits (24-28/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (95.7% purity) in methyl cellulose (400 cP) at 0, 25, 50, or 100 mg/kg/day on gestation days 7-28. Maternal

examinations included clinical signs of toxicity, body weights, food consumption, ovaries, and uterine content. Fetal examinations included evaluation of sex, fetal body weight, crown-rump length, and the incidence of external, visceral, and skeletal malformations. Three high dose females terminated their pregnancies on gestation day 22 or 24 following marked body weight losses (12.7-18.3% decreases relative to body weight at the start of the exposure period) and reduced food consumption. One female in the low dose group was discovered dead on gestation day 28 (not considered treatment-related by the study authors, possibly resulting from a gavage error). Mid and high dose dams exhibited marked to severe decreases in food consumption and increased incidences of decreased defecation, mucoid feces (high dose only), and brown material on the facial area. The decreased food consumption correlated with decreased body weights and body weight gains in mid and high dose females during the dosing period. During the period after dosing and prior to sacrifice, mid and high dose group females exhibited mean body weight gains and food consumption comparable to or greater than the control group. At sacrifice, mid and high dose dams exhibited decreased mean net body weight changes and high dose dams exhibited decreased mean gravid uterine weight. Mid and high dose dams exhibited increased mean absolute and relative liver weights. Treatment increased mean post-implantation losses and correspondingly decreased the mean litter proportion of viable fetuses in the high dose group. Mean fetal body weights decreased 9.9% and 22.2% in the mid and high dose groups, respectively, relative to the concurrent control group. Treatment did not increase the incidence of external, visceral, or skeletal malformations. The authors identified a maternal toxicity NOAEL of 25 mg/kg/day based on the decreased body weights and food consumption and increased liver weights at ≥ 50 mg/kg/day, and a developmental toxicity NOAEL of 25 mg/kg/day based on decreased fetal body weights at ≥ 50 mg/kg/day and increased post-implantation losses at 100 mg/kg/day (Klimisch Score 1, reliable without restriction).

- o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A GLP-compliant U.S. EPA OPPTS 890.1450 pubertal study was performed with juvenile female Sprague-Dawley rats (15/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (91% purity) in corn oil at 0, 250, or 500 mg/kg/day for 21 days (postnatal days 22 to 42 or 43). The animals were evaluated for clinical signs of toxicity, body weights, vaginal opening, estrous cyclicity, thyroid hormone levels (T4 and TSH), and histopathology (kidney, thyroid, ovary, and uterus). Treatment-related clinical signs of toxicity included salivation prior to dosing, clear material around the mouth approximately two hours after dosing, and yellow material around the urogenital region (high dose only). Decreased mean body weight gains were identified during the first two (low dose) or three (high dose) days of dosing, resulting in mean body weights that were 8.73% and 14.83% less than the control group for the low and high dose groups, respectively, during the treatment period. Vaginal opening was achieved at an earlier date for the high dose group (33.2 days) than the concurrent control group (35.2 days), and lower body weights were noted for females in both dose groups at the time of vaginal opening. Treatment increased the age at first estrus for the high dose group (39.2 days) compared to the concurrent controls (36.3 days), and a lower number of animals were cycling by the end of study period relative to the control group (estrous cycle lengths could not be evaluated). Treatment in both dose groups increased serum TSH and cholesterol levels and decreased serum T4, AST, and triglyceride levels. High dose females also exhibited increased total bilirubin and gamma-glutamyl transferase (GGT) levels. High dose females exhibited decreased ovary weights, and mid and high dose females exhibited decreased uterine (blotted and unblotted) weights and increased liver, kidney, and thyroid weights. Treatment-

related histopathological alterations included lower colloid area and increased follicular cell height in thyroid glands of mid and high dose females, and vacuolation of the liver, absence of corpora lutea with increased tertiary follicles in the ovaries (i.e., non-cycling), and immature uterus of high dose females. The authors postulated that the increased liver weights, alterations to thyroid gland histopathology and T4 and TSH levels were secondary to hepatomegaly, but the liver histopathology was not evaluated. The authors concluded that oral dosing with N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) produced evidence of endocrine-mediated effects on pubertal development and thyroid function in juvenal female rats (Klimisch Score 1, reliable without restriction).

- o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A GLP-compliant OPPTS 890.1500 Endocrine Disruption test was performed with juvenile male Sprague-Dawley rats (15/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (91.0% purity) in corn oil at 250 or 500 mg/kg/day for 30 days (postnatal days 23 to 53 or 54). The males were evaluated for clinical signs of toxicity and body weights, balanopreputial separation (beginning on postnatal day 30), serum T4, TSH, and testosterone levels, and histopathology of the kidney, thyroid, testis, and epididymis. One high dose male was euthanized *in extremis* on postnatal day 25 due to severe body weight loss. Treatment-related clinical signs of toxicity included salivation prior to dosing and red and/or clear material around the mouth approximately two hours after dosing. Decreased body weight gains were noted in both dose groups, with mean final body weights for the low and high dose group animals up to 8.69% and 22.33% lower than the control group, respectively. High dose males exhibited a delayed mean age of balanopreputial separation attainment, and lower body weights on the day of attainment of balanopreputial separation was noted for both dose groups. The authors attributed these findings to the decreased body weights for these groups. High dose males exhibited higher GGT and ALT activities, and mid and high dose males exhibited decreased T4 and testosterone and increased TSH levels. Treatment-related organ weight changes included increased liver weights and decreased testes, epididymides, prostate, and seminal vesicle/coagulating gland weights in males of both dose groups. Treatment-related histopathological changes were limited to lower colloid area and increased follicular cell height in the thyroid gland in both dose groups. The authors considered the histopathological changes in the thyroid gland, increased liver weights, TSH, ALT, and GGT levels, and decreased T4 to be secondary to hepatomegaly, although the histopathology of the liver was not evaluated. Additionally, the authors attributed the decreased testosterone levels and male reproductive organ weights to be secondary to systemic stress (decreased body weights). "Therefore, there was no clear evidence of any direct test-substance-related endocrine effects." (Klimisch Score 1, reliable without restriction)
- o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A GLP-compliant OPPTS 890.1450 pubertal development and thyroid function test with juvenile female Sprague-Dawley rats (15/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, purity not specified) in corn oil at 10, 100, or 300 mg/kg/day for 21 days is presented in the REACH dossier. However, no results are provided for this test.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Moderate for endocrine activity based on altered female pubertal development in rats exposed to the surrogate. In addition, *in vitro* data from the EDSP21 program and ToxCast modeling indicate that the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) and/or its metabolites may be

estrogen/androgen receptor antagonists/agonists. However, there does not appear to be endocrine-mediated carcinogenicity, reproductive or developmental toxicity, or systemic toxicity that warrant raising the final score to High. While the score for reproductive toxicity endpoint is High, there is no evidence that the critical reproductive effect, dystocia, is mediated via endocrine disruption.

GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when there is evidence of endocrine activity and there are no linked health effects that warrant raising the score (CPA 2018b). The confidence in the score is high as estrogen-mediated effects on female pubertal development were observed *in vivo*.

- 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: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):*
A GLP-compliant U.S. EPA OPPTS 890.1450 pubertal study was performed with juvenile female Sprague-Dawley rats (15/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (91% purity) in corn oil at 0, 250, or 500 mg/kg/day for 21 days (postnatal days 22 to 42 or 43). The animals were evaluated for clinical signs of toxicity, body weights, vaginal opening, estrous cyclicity, thyroid hormone levels (T4 and TSH), and histopathology (kidney, thyroid, ovary, and uterus). Treatment-related clinical signs of toxicity included salivation prior to dosing, clear material around the mouth approximately two hours after dosing, and yellow material around the urogenital region (high dose only). Decreased mean body weight gains were identified during the first two (low dose) or three (high dose) days of dosing, resulting in mean body weights that were 8.73% and 14.83% less than the control group for the low and high dose groups, respectively, during the treatment period. Vaginal opening was achieved at an earlier date for the high dose group (33.2 days) than the concurrent control group (35.2 days), and lower body weights were noted for females in both dose groups at the time of vaginal opening. Treatment increased the age at first estrus for the high dose group (39.2 days) compared to the concurrent controls (36.3 days), and a lower number of animals were cycling by the end of study period relative to the control group (estrous cycle lengths could not be evaluated). Treatment in both dose groups increased serum TSH and cholesterol levels and decreased serum T4, AST< and triglyceride levels. High dose females also exhibited increased total bilirubin and gamma-glutamyl transferase (GGT) levels. High dose females exhibited decreased ovary weights, and mid and high dose females exhibited decreased uterine (blotted and unblotted) weights and increased liver, kidney, and thyroid weights. Treatment-related histopathological alterations included lower colloid area and increased follicular cell height in thyroid glands of mid and high dose females, and vacuolation of the liver, absence of corpora lutea with increased tertiary follicles in the ovaries (i.e., non-cycling), and immature uterus of high dose females. The authors postulated that the increased liver weights, alterations to thyroid gland histopathology and T4 and TSH levels were secondary to hepatomegaly, but the liver histopathology was not evaluated. The authors concluded that oral dosing with N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) produced evidence of endocrine-mediated effects on pubertal development and thyroid function in juvenile female rats (Klimisch Score 1, reliable without restriction).
 - *Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):*
A GLP-compliant OPPTS 890.1500 Endocrine Disruption test was performed with juvenile male Sprague-Dawley rats (15/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (91.0% purity) in corn oil at 250 or 500 mg/kg/day

for 30 days (postnatal days 23 to 53 or 54). The males were evaluated for clinical signs of toxicity and body weights, balanopreputial separation (beginning on postnatal day 30), serum T4, TSH, and testosterone levels, and histopathology of the kidney, thyroid, testis, and epididymis. One high dose male was euthanized *in extremis* on postnatal day 25 due to severe body weight loss. Treatment-related clinical signs of toxicity included salivation prior to dosing and red and/or clear material around the mouth approximately two hours after dosing. Decreased body weight gains were noted in both dose groups, with mean final body weights for the low and high dose group animals up to 8.69% and 22.33% lower than the control group, respectively. High dose males exhibited a delayed mean age of balanopreputial separation attainment, and lower body weights on the day of attainment of balanopreputial separation was noted for both dose groups. The authors attributed these findings to the decreased body weights for these groups. High dose males exhibited higher GGT and ALT activities, and mid and high dose males exhibited decreased T4 and testosterone and increased TSH levels. Treatment-related organ weight changes included increased liver weights and decreased testes, epididymides, prostate, and seminal vesicle/coagulating gland weights in males of both dose groups. Treatment-related histopathological changes were limited to lower colloid area and increased follicular cell height in the thyroid gland in both dose groups. The authors considered the histopathological changes in the thyroid gland, increased liver weights, TSH, ALT, and GGT levels, and decreased T4 to be secondary to hepatomegaly, although the histopathology of the liver was not evaluated. Additionally, the authors attributed the decreased testosterone levels and male reproductive organ weights to be secondary to systemic stress (decreased body weights). “Therefore, there was no clear evidence of any direct test-substance-related endocrine effects.” (Klimisch Score 1, reliable without restriction)

- U.S. EPA 2021b
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was active in 4/6 estrogen receptor (ER) assays (positive in 4 antagonist assays, negative in two agonist assays), 7/8 androgen receptor (AR) assays (positive in 6 antagonist assays and in 1/2 agonist assays), 2/2 steroidogenesis assays, and 2/6 thyroid receptor assays (positive in 2/3 antagonist assays) performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (Appendix D).
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was predicted to be inactive for estrogen receptor agonism but active (very weak) for estrogen receptor antagonism and binding using the CERAPP Potency Level (from literature) model. It was predicted to be inactive for estrogen receptor agonism, antagonism, and binding using the CERAPP Potency Level (consensus) model. It was also predicted to be inactive for androgen receptor agonism and binding but active for androgen receptor antagonism using the COMPARA (Consensus) model in ToxCast (Appendix E).
- VEGA 2021
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) is outside of the applicability domain for the VEGA Estrogen Receptor Relative Binding Affinity model (IRFMN) (Appendix F)
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) is predicted to be possibly non-active in the Estrogen Receptor-mediated effect (IRFMN/CERAPP) 1.0.0 model with strong reliability (global applicability domain (AD) index = 0.86, similarity index = 0.739, accuracy index = 1, concordance index = 1) (Appendix F).

- N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was predicted to be non-active in the Androgen Receptor-mediated effect (IRFMN/COMPARA) 1.0.0 model with moderate reliability (global AD Index = 0.727, similarity index = 0.748, accuracy index = 0.499, concordance index = 1) (VEGA 2019) (Appendix F).
- DTU 2021
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) is not predicted to bind to the estrogen receptor as it lacks hydroxyl and amine groups, but its metabolites predicted via *in vivo* rat metabolism and rat liver S9 metabolism are expected to bind strongly to the estrogen receptor as they contain hydroxyl groups (Appendix G).
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was predicted to be negative and in domain for the model battery for estrogen receptor α -binding with the full training set (composed of negative and in domain results by Leadscape and SciQSAR) (Appendix G).

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

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

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Moderate for acute toxicity based on oral LD₅₀ values as low as 893 mg/kg in rats for the surrogate. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when oral LD₅₀ values are > 300 to 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on a strong 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
 - *Oral*: LD₅₀ (unspecified species) > 2,000 mg/kg (males and females).
 - *Dermal*: LD₅₀ (unspecified species) > 2,000 mg/kg (males and females).
- Flexsys 2007
 - *Oral*: LD₅₀ (rat) > 3,000 mg/kg.
 - *Dermal*: LD₅₀ (rabbit) > 3,000 mg/kg.
- UNEP 2005, ECHA 2021a
 - *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)*: LD₅₀ (Sprague-Dawley rats) = 893 mg/kg (females), 1,005 mg/kg (males) (GLP-compliant, OECD Guideline 401) (Klimisch Score 1, reliable without restriction).
 - Corn oil was used as the vehicle with 99% purity test substance.
 - *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)*: LD₅₀ (Sprague-Dawley rats) = 3,340 (males and females) (Klimisch Score 2, reliable without restriction).
 - No vehicle was used (test substance purity not specified).
 - *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)*: LD₅₀ (Sprague-Dawley rats) = 3,580 mg/kg (males and females) (Klimisch Score 2, reliable without restriction).
 - No vehicle was used with the 95.7% purity test substance.
 - *Dermal: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)*: LD₅₀ (New Zealand White rabbits) > 7,940 mg/kg (males and females)

- No vehicle was used with the 95.7% purity substance warmed to 115°F to liquefy and applied under semi-occlusive dressing for 24 hours.
- ECHA 2021a
 - *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* LD₅₀ (Sprague-Dawley rats) > 5,000 mg/kg (males and females) (GLP-compliant, EPA OTS 798.1175) (Klimisch Score 1, reliable without restriction).
 - No vehicle was used with the 97.6% purity test substance.
 - *Dermal: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* LD₅₀ (Wistar rats) > 2,000 mg/kg (males and females) (GLP-compliant, OECD Guideline 434) (Klimisch Score 4, not assignable).
 - No vehicle was used with the test substance (Dusantox 6PPD, purity not specified) under semi-occlusive dressing for 24 hours.
 - Additional acute oral toxicity tests are presented in the REACH dossier for N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD). However, they were assigned Klimisch Scores of 3 (not reliable) or 4 (not assignable); therefore, ToxServices did not include the results of these studies in the current assessment.
- In summary, dermal LD₅₀ values are > 2,000 mg/kg in rabbits and/or rats for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) and the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD). Oral LD₅₀ values are > 2,000 mg/kg for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI). The oral LD₅₀ values for the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) are more variable depending on whether a vehicle was used. In the absence of a vehicle, oral LD₅₀s range from 3,340 mg/kg to > 5,000 mg/kg. In contrast, when olive oil is used as the vehicle, the oral LD₅₀s are 893-1,005 mg/kg. Therefore, it is likely that the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD), and possibly N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI), is more bioavailable in a lipid/fat rich media due to its lipophilicity (log K_{ow} = 2.82-4.68). Consequently, ToxServices assigned the score for this endpoint based on the lower LD₅₀ of 893 mg/kg for the surrogate.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Moderate for systemic toxicity (single dose) based on ToxServices classifying it as a Category 3 specific target organ toxicant following single exposures for respiratory irritation under GHS criteria. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified as GHS Category 3 specific target organ toxicants following single exposures for respiratory irritation (CPA 2018b). The confidence in the score is low as no measured data were identified and the GHS classification is based on a statement provided in an MSDS.

- Authoritative and Screening Lists
 - *Authoritative:* Not present on any authoritative lists for this endpoint.
 - *Screening:* Not present on any screening lists for this endpoint.
- Flexsys 2007
 - “May cause mild respiratory irritation.”
- UNEP 2005, ECHA 2021a
 - *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* In the GLP-compliant OECD Guideline 401 acute oral toxicity test that identified oral LD₅₀s of 893-1,000 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included decreased fecal volume at ≥ 500 mg/kg; diarrhea, hypothermia, prone position, bradypnea (abnormally slow breathing rate), and hypoactivity at ≥ 1,000

- mg/kg, and abnormal gait (males only), lacrimation (females only), and weakness of limbs (females only) at 2,000 mg/kg. At necropsy, pathological lesions were identified in the respiratory tract and digestive organs (dose levels not specified). The tested doses were 250, 500 1000, and 2,000 mg/kg. Mortality was observed at the two highest doses only. No further details were provided (Klimisch Score 1, reliable without restriction).
- o *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* In the acute oral toxicity study that identified an oral LD₅₀ of 3,340 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included collapse 15-30 minutes after dosing with subsequent recovery, and loss of appetite, salivation, severe diarrhea, and dyspnea (difficult or labored breathing). At necropsy, renal and liver congestion and inflammation of the gastric mucosa were identified (unclear what dose level these findings were identified at and whether findings were for decedents or survivors). The tested doses were 2,510, 3,160, 3,980, and 5,010 mg/kg (Klimisch Score 2, reliable without restriction).
 - o *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* In the acute oral toxicity test that identified an oral LD₅₀ of 3,580 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included decreased appetite and activity lasting 2-5 days, diarrhea, weakness, ocular discharge, and collapse. At necropsy, some survivors exhibited slight discoloration of the liver. The tested doses were 2,510, 3,160, 3,980, 5,010, and 6,310 mg/kg (Klimisch Score 2, reliable without restriction).
 - o *Dermal: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* In the acute dermal toxicity test that identified a dermal LD₅₀ > 7,940 mg/kg in male and female New Zealand White rabbits, clinical signs of toxicity included decreased activity and appetites for 3-7 days. Treatment did not affect gross pathological findings. The tested doses were 3,160, 5,010, and 7,940 mg/kg (Klimisch Score 2, reliable without restriction).
- ECHA 2021a
 - o *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* In the GLP-compliant, EPA OTS 798.1175 acute oral toxicity test that identified an oral LD₅₀ > 5,000 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included reduced fecal output, piloerection, rough coat, urine/fecal stains, dark material around the facial region, and diarrhea/soft stools. Reduced body weights were identified for one surviving male and 3 surviving females, while the remaining surviving animals exhibited body weight gains. At necropsy, the most notable finding was hard (rock-like), black material in the stomach of decedents and survivors. The only dose tested was 5,000 mg/kg (Klimisch Score 1, reliable without restriction).
 - o *Dermal: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* No details on clinical signs of toxicity, body weights, or gross pathological findings were provided for the study that identified a dermal LD₅₀ > 2,000 mg/kg in Wistar rats. The only dose tested was 2,000 mg/kg (Klimisch Score 4, not assignable).
 - In summary, only one study evaluated doses less than the GHS oral guidance value of 2,000 mg/kg (UN 2021). This study identified significantly adverse clinical signs of toxicity (morbidity) at doses ≥ 1,000 mg/kg for the surrogate 6PPD. However, mortality also occurred at ≥ 1,000 mg/kg. Section 3.8.1.1 of the GHS criteria defines classifiable toxicity for this endpoint as non-lethal toxic effects on target organs. Therefore, ToxServices did not use these observations as basis of classification for this endpoint.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Moderate for systemic toxicity (repeated dose) based on ToxServices classifying the surrogate as a Category 2 specific target organ toxicant following repeated oral doses under GHS criteria for effects on the liver and blood system. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when they are classified as GHS Category 2 specific target organ toxicants following repeated oral doses (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on a strong 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
 - *Oral*: A NOAEL and NOEL of 15 mg/kg/day are presented in the REACH dossier for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) without any context.
- UNEP 2005, ECHA 2021a
 - *Oral*: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A GLP-compliant repeated dose toxicity test conducted according to the Japanese Guideline for 28-day Repeat Dose Toxicity Testing of Chemicals was performed with Sprague-Dawley rats (5/sex/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (99% purity) in corn oil at 0, 4, 20, or 100 mg/kg/day for 28 days. Additional groups of 5 animals/sex/group were dosed with 0 or 100 mg/kg/day for 28 days and then maintained for an additional 14 days without dosing. The animals were evaluated for body weight, clinical chemistry, hematology, urinalysis, gross pathology, and histopathology. Treatment did not affect body weights. Statistically significantly altered clinical chemistry parameters at the end of the exposure period included increased total protein and decreased inorganic phosphate in mid dose females; increased creatinine, total protein, total cholesterol and calcium and decreased albumin/globulin in high dose males; and increased total protein and albumin and decreased inorganic phosphate in high dose females. At the end of the recovery period, high dose males exhibited statistically significantly increased triglyceride levels. Statistically significantly altered hematology parameters at the end of the exposure period included increased platelets and decreased hematocrit in high dose males, and increased platelets and decreased hemoglobin, hematocrit, mean corpuscular volume (MCV), prothrombin time, and activated partial thromboplastin time in high dose females. At the end of the recovery period, high dose males exhibited significantly decreased MCV, mean corpuscular hemoglobin (MCH), and hematocrits and increased platelets, and high dose females exhibited decreased hemoglobin, hematocrit, MCH, and MCV. High dose males and females exhibited increased urinary proteins levels (time point not specified), and increased liver weights at the end of the exposure period. The increased liver weights were still evident in high dose females at the end of the recovery period. Reversible liver enlargement was identified for two males and one female in the high dose groups, and reversible periportal fatty change was evident for mid and high dose females and high dose males. The authors identified a NOAEL of 20 mg/kg/day based on effects to the liver and hematology and clinical chemistry parameters at 100 mg/kg/day (Klimisch Score 1, reliable without restriction).
 - As this study had an exposure period less than 90 days, ToxServices adjusted the GHS oral guidance values of 10 and 100 mg/kg/day (UN 2021) by a factor of 3 (28 days is approximately one-third of 90 days) to 30 and 300 mg/kg/day, respectively.

Since the LOAEL of 100 mg/kg/day is between the adjusted guidance values, ToxServices classified N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) as a GHS Category 2 specific target organ toxicant following repeated oral dosing based on effects to the liver and blood system.

- o *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A non-GLP-compliant chronic feeding study conducted in a manner similar to OECD Guideline 452 was performed with Sprague-Dawley rats (70/sex/group) provided diets containing N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (100% active ingredient as Santoflex 13) at 0, 50, 250, or 1,500 ppm (contributing doses of 2.6, 13.5, and 84.8 mg/kg/day for males and 3.2, 16.5, and 109.5 mg/kg/day for females, respectively). After 12 months, 20 rats/sex/group were sacrificed and evaluated for treatment-related effects. The surviving animals were sacrificed after 24 months. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology. High dose males and females and mid dose females consistently exhibited decreased mean body weights. These groups exhibited increased food consumption values, suggesting a decreased food utilization for these animals. Treatment slightly altered hematology parameters in the high dose group, including decreased hemoglobin, hematocrit, erythrocyte counts (females only), MCV, and MCH, and increased platelet counts. Treatment also significantly increased cholesterol levels in high dose males and females. At necropsy, mean absolute and relative kidney weights increased in high dose males and females sacrificed after 12 months but not after 24 months. The severity but not the incidence of chronic nephropathy increased in high dose males and females sacrificed after 12 and 24 months. The mean absolute and relative liver weights increased in mid dose males and females at termination and in high dose males and females at the 12- and 24-month sacrifices. High dose females exhibited increased incidences of cytoplasmic vacuolization of the liver and pigment in the hepatocytes and reticuloendothelial cells. No histopathological alterations were identified in the livers of high dose males or mid dose males or females. Treated males had a slightly increased incidence of thyroid follicular cell hyperplasia. Treatment increased the mean absolute and relative spleen weights of high dose males sacrificed after 12 months but not 24 months. The authors identified a NOEL/NOAEL of 50 ppm (equivalent to 2.6-3 mg/kg/day) and LOEL/LOAEL of 250 ppm (equivalent to 13.5-16.5 mg/kg/day) based on decreased body weights and increased food consumption in mid dose females and increased liver weights for both sexes.
 - The REACH dossier authors assigned this study a Klimisch Score 2 (reliable with restrictions). In contrast, the SIDS dossier authors assigned this study a Klimisch Score 4 (not assignable).
 - Since the exposure duration was greater than 90 days, ToxServices adjusted the GHS oral guidance values of 10 and 100 mg/kg/day by a factor of 8 (90 days is approximately eight time less than 24 months or 730 days) to 1.25 mg/kg/day and 12.5 mg/kg/day, respectively. As the LOEL/LOAEL of 13.5-16.5 mg/kg/day was greater than the adjusted guidance values, ToxServices did not classify N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) as a specific target organ toxicant following repeated doses based on the results of this study.
- o *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A GLP-compliant, OECD Guideline 421 reproduction/developmental toxicity screening test was performed with Crj: CD(SD) rats (12/sex/group) administered gavage doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (99.4% purity) in corn oil at 0, 6, 25, or 100 mg/kg/day. Males were dosed for 48 days, and females were

dosed for 14 days prior to mating until lactation/postnatal day 3. Treatment did not affect body weight gain, and food consumption rates increased intermittently in high dose males and in females in all dose groups during lactation only. In the low dose group, histopathological changes were limited to slightly cellular infiltration of lymphocytes in 4/12 males (organ not specified, presumably liver). In the mid dose group, treatment increased the incidence of salivation and vacuolar liver degeneration in males, increased absolute liver weights in females, and increased relative liver weights in males and females. In the high dose group, one dam died on gestation day 23 and both sexes exhibited increased incidences of salivation, liver enlargement, increased relative and absolute liver weights. High dose males also exhibited increased absolute and relative adrenal weights and an increased incidence of vacuolar liver degeneration. The authors identified a NOAEL of 6 mg/kg/day based on increased liver weights, salivation, and vacuolar liver degeneration identified at 25 mg/kg/day (Klimisch Score 1, reliable without restriction).

- As the exposure duration was less than 90 days, ToxServices adjusted the GHS oral guidance values of 10 and 100 mg/kg/day (UN 2021) by a factor of 2 (48 days is approximately half of 90 days) to 20 and 200 mg/kg/day, respectively. Since the LOAEL of 25 mg/kg/day is between the adjusted guidance values, ToxServices classified N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) as a GHS Category 2 specific target organ toxicant following repeated oral dosing based on effects to the liver.
- o *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A non-GLP-compliant chronic feeding study was performed with Charles River (CD Outbred) rats (50/sex/group) provided diets containing N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, purity not specified) at 0, 100, 300, or 1,000 ppm (contributing doses of 0, 8, 23, or 75 mg/kg/day) for 24 months. Treatment did not adversely affect survival, frequency of clinical signs, clinical chemistry or urinalysis parameters, or gross or histopathological findings relative to the concurrent control group. High dose rats exhibited decreased body weights and body weight gains, which correlated with decreased food consumption during the first four and two weeks of treatment for males and females, respectively. Treatment decreased erythrocyte counts in high dose males at 3 months and high dose females at 3, 6, and 12 months but not at later times points. Treatment significantly decreased hematocrit values in high dose males at 3 and 12 months and in high dose females at 3, 6, and 12 months, and slightly increased hematocrit values in high dose males and females at 18 and 24 months. Treatment-related organ weight changes included decreased absolute and relative kidney weights in high dose females, increased absolute and relative liver weights in high dose males, and decreased absolute and relative spleen weights in high dose females. The authors identified a NOAEL of 300 ppm (23 mg/kg/day) based on altered body weights, hematology parameters, and organ weights at 1,000 ppm (75 mg/kg/day) (Klimisch Score 2, reliable with restrictions).
- o *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):* A GLP-compliant subchronic repeated dose toxicity test was performed with Sprague-Dawley rats (25/sex/group) provided diets containing N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13, 97.1% purity) in diet at 0, 250, 1,000, or 2,500 ppm (contributing doses of 15.7, 62.3, and 153.8 mg/kg/day for males and 18.5, 75.0, and 172.1 mg/kg/day for females, respectively) for 13 weeks. Treatment did not adversely affect survival, clinical signs of toxicity, ophthalmoscopic findings. High dose females and mid and high dose males exhibited decreased body weight gains from the start of the exposure period. Terminal body weights decreased in a dose-related manner, with high dose males and females having terminal body weights that were 87% and 90%,

respectively, of the concurrent controls. Decreased body weight gains correlated with decreased food consumption values for mid and high dose males and high dose females. In mid and high dose males and females, treatment increased albumin, globulin, total protein, calcium, and cholesterol levels and decreased creatine, aspartate aminotransferase (AST, SGOT), alanine aminotransferase (AST, SGPT), and blood urea nitrogen (BUN). Mid and high dose males also exhibited increased bilirubin levels. Treatment induced mild anemia and thrombocytosis and decreased red blood cell counts, hemoglobin (Hb), MCV, hematocrit (HCT), MCH, mean corpuscular hemoglobin concentration (MCHC) in mid and high dose animals. Low dose females also exhibited decreased lymphocytes and white blood cell count and slight anemia during the interim sampling period only. Increased absolute liver weights were evident in high dose males and high dose females, and increased relative liver weights were identified in mid and high dose males and females in all treated groups. Absolute spleen weights significantly decreased in high dose males, while relative spleen weights increased in high dose males. High dose males also exhibited statistically significantly decreased absolute testes weights, but relative testes weights were unaffected by the treatment. Relative brain weights increased in mid and high dose males and high dose females, and relative kidney weights increased in mid and high dose females. The authors identified a NOAEL of 250 ppm (15.7-18.5 mg/kg/day) based on reduced body weight gain, mild anemia, and increased liver weights detected at 1,000 ppm (62.3-75 mg/kg/day)

- The REACH dossier authors assigned this study a Klimisch Score 1 (reliable without restriction). In contrast, the SIDS dossier authors assigned this study a Klimisch Score 2 (reliable with restrictions).
- As the LOAEL of 62.3-75 mg/kg/day is between the GHS oral guidance values of 10 and 100 mg/kg/day (UN 2021), ToxServices classified N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) as a GHS Category 2 specific target organ toxicant following repeated oral dosing based on effects to the liver and blood system.
- Additional repeated oral dose toxicity studies and one repeated inhalation exposure study are presented in the REACH and SIDS dossiers for N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD). However, they were assigned Klimisch Scores of 3 (not reliable) or 4 (not assignable) and/or had limited levels of detail available. Therefore, ToxServices did not include the results of these studies in the current assessment.
- In summary, multiple repeated oral dose toxicity studies identified the liver and blood system as the target organs for the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD). Based on the LOAELs for the 28-day and 90-day studies and the OECD Guideline 421 study, ToxServices classified N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) as a Category 2 specific target organ toxicant following repeated oral doses under GHS criteria (UN 2021).

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Moderate for neurotoxicity (single dose) based on ToxServices classifying the surrogate as a Category 3 specific target organ toxicant following single exposures for narcotic effects under GHS criteria. GreenScreen[®] criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified as GHS Category 3 specific target organ toxicants following single exposures for narcotic effects (CPA 2018b). The confidence in the score is low as it is not clear if the observed effects were specific neurotoxicity or just a manifestation of general toxicity and weakness after receiving a large dose of a chemical.

- Authoritative and Screening Lists
 - *Authoritative*: Not present on any authoritative lists for this endpoint.
 - *Screening*: Not present on any screening lists for this endpoint.
- UNEP 2005, ECHA 2021a
 - *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)*: In the GLP-compliant OECD Guideline 401 acute oral toxicity test that identified oral LD₅₀s of 893-1,000 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included decreased fecal volume at ≥ 500 mg/kg; diarrhea, hypothermia, prone position, bradypnea (abnormally slow breathing rate), and hypoactivity at ≥ 1,000 mg/kg, and abnormal gait (males only), lacrimation (females only), and weakness of limbs (females only) at 2,000 mg/kg (Klimisch Score 1, reliable without restriction).
 - *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)*: In the acute oral toxicity study that identified an oral LD₅₀ of 3,340 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included collapse 15-30 minutes after dosing with subsequent recovery, and loss of appetite, salivation, and severe diarrhea (Klimisch Score 2, reliable without restriction).
 - *Oral: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)*: In the acute oral toxicity test that identified an oral LD₅₀ of 3,580 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included decreased appetite and activity lasting 2-5 days, diarrhea, weakness, and collapse (Klimisch Score 2, reliable without restriction).
 - *Dermal: Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8)*: In the acute dermal toxicity test that identified a dermal LD₅₀ > 7,940 mg/kg in male and female New Zealand White rabbits, clinical signs of toxicity included decreased activity and appetites for 3-7 days (Klimisch Score 2, reliable without restriction).
- In summary, single oral or dermal doses of the surrogate N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) produced signs of transient narcotic effects, including decreased activity, hypothermia, weakness of limbs, and abnormal gait. Therefore, ToxServices classified it as a specific target organ toxicant following single exposures for narcotic effects under GHS criteria (UN 2021).

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of 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.
- ToxServices identified no data for this endpoint.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of High for skin sensitization based on ToxServices classifying the surrogate as a Category 1A skin sensitizer under GHS criteria. GreenScreen® criteria classify chemicals as a High hazard for skin sensitization when they are classified as GHS Category 1A skin sensitizers (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on a strong 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 a guinea pig skin sensitization test (maximization or Buehler test not specified), no positive skin sensitization reactions were identified in any of the 20 treatment group animals following readings at 24 or 48 hours. No further details were provided.
- ECHA 2021a
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A guinea pig maximization test was performed with female Hartley guinea pigs (4/group) administered dermal doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (purity not specified). The induction doses were 500 ppm (0.05%) in acetone and the challenge doses were 50 or 5,000 ppm in acetone under occlusive coverage. At 48 hours after the challenge dose, 4/4 animals exhibited positive skin reactions towards the 50 and 5,000 ppm doses. Therefore, the authors concluded that N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was sensitizing to the skin under the tested conditions (Klimisch Score 2, reliable with restrictions).
 - Based on 100% of the animals responding following an intradermal dose of 0.05%, N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) warrants classification as a GHS Category 1A skin sensitizer. GHS criteria define Category 1A skin sensitizers as chemicals that produce positive reactions $\geq 30\%$ animals at $\leq 0.1\%$ intradermal doses (UN 2021).
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A local lymph node assay was performed with female Balb/c mice administered topical applications of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (purity and vehicle not specified) at 0%, 0.1%, 0.3%, 1%, or 3%. The stimulation indices were 2.34 at 1% and 5.06 at 3%. As the concentrations tested were non-irritating, the authors concluded that N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was sensitizing to the skin under the tested conditions (Klimisch Score 2, reliable with restrictions).
 - As the authors did not identify an EC3, ToxServices calculated the EC3 as 1.49% using the linear interpolation method of Ryan et al. (2007). The EC3 of 1.49% is less than the GHS guidance value of 2% (UN 2021), warranting classification as a GHS Category 1A skin sensitizer.
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A GLP-compliant, OECD Guideline 429 local lymph node assay was performed with female CBA mice (4/group) administered topical applications of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Dusantox 6PPD, purity not specified) in acetone/olive oil (4:1 v/v) at 10%, 25%, or 50%. The stimulation indices were 1.55, 12.37, and 12.38 for the 10%, 25%, and 50% solutions, respectively. The authors calculated an EC3 of 12.06% and concluded that N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was moderately sensitizing to the skin under the tested conditions (This study was reported in the REACH dossier without a Klimisch Score).
 - As the EC3 of 12.06% is greater than the GHS guidance value of 2% (UN 2021), N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) warrants classification as a GHS Category 1B skin sensitizer.
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A non-GLP-compliant guinea pig maximization test was performed with guinea pigs (15/group, strain not specified) administered dermal doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Vulkanox 4020). The induction doses were administered as intradermal injection doses of 1% test substance in polyethylene glycol and topical applications of 2% test substance in polyethylene glycol. The challenge dose was

applied as a topical application of 12.5% or 25% test substance in polyethylene glycol under occlusive dressing. Following challenge with 12.5% test substance, 6/15 and 3/15 animals exhibited positive dermal reactions at 24 and 48 hours respectively compared to 0/15 in the negative control at both time points. Following challenge with 25% test substance, 15/15, and 14/15 animals exhibited positive dermal reactions at 24 and 48 hours, respectively, compared to 2/15 negative control animals at both time points.

- Based on 100% of the animals responding following an intradermal dose of 1%, N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) warrants classification as a GHS Category 1A skin sensitizer. GHS criteria define Category 1A skin sensitizers as chemicals that produce positive reactions $\geq 60\%$ animals at $> 0.1\%$ to $\leq 1\%$ intradermal doses (UN 2021).
- UNEP 2005, ECHA 2021a
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
A guinea pig maximization test was performed with female Hartley guinea pigs (20/group) administered dermal doses of N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (purity not specified). The induction doses were applied as intradermal injections of 0.5% test substance in olive oil and a topical application of 1% test substance in Vaseline. The challenge dose was applied at topical applications of 0.05% or 0.5% in Vaseline. The type of coverage was not specified. At 48 hours after the challenge dose, the 0.05% challenge produced 10/20 positive reactions compared to 0/20 for the negative control and the 0.5% challenge produced 18/20 positive reactions compared to 4/20 for the negative control. The authors concluded that N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was sensitizing to the skin under the tested conditions (Klimisch Score 2, reliable with restrictions).
 - Based on 50%-90% of the animals responding following an intradermal dose of 0.5%, N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) warrants classification as a GHS Category 1A skin sensitizer. GHS criteria define Category 1A skin sensitizers as chemicals that produce positive reactions $\geq 60\%$ animals at $> 0.1\%$ to $\leq 1\%$ intradermal doses (UN 2021).
- UNEP 2005
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8):
Healthy volunteers not previously exposed to test rubber formulations had at most a low rate of sensitization towards N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD), whereas individuals previously sensitized to rubber samples exhibited a higher rate of sensitization towards this chemical: positive sensitization results were identified in 17/50, 16/50, 4/50, and 5/50 previously exposed individuals participating in repeated insult patch tests.
- As the results from the majority of animal tests support classification of the surrogate N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) as a GHS Category 1A skin sensitizer, ToxServices classified it as a GHS Category 1A skin sensitizer and assigned a high hazard for this endpoint.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Data Gap for respiratory sensitization based on insufficient data. ToxServices did not consider N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) an appropriate surrogate as it contains a structural alert for respiratory sensitization (i.e., phenylenediamines) as identified by OECD Toolbox.

- 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
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) does not contain any structural alerts for respiratory sensitization (Appendix H).
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) 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). N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) does not contain any structural alerts, but is expected to be a skin sensitizer based on positive results for the surrogate. According to the ECHA guidance, the positive skin sensitization results in animals and lack of structural alerts and evidence of respiratory sensitization indicate that there is insufficient positive data for the chemical to be classified as a respiratory sensitizer. However, the guidance requires negative skin sensitization data in order to conclude that the chemical is not a respiratory sensitizer. GreenScreen® criteria require negative data in order to assign a Low (i.e., a lack of alerts is not sufficient). Due to the positive results for skin sensitization and uncertainty regarding whether the mechanisms of sensitization could correspond to respiratory sensitization, a Data Gap was assigned.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Low for skin irritation/corrosivity based on ToxServices not classifying it as a skin irritant under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
 - *Authoritative*: Not present on any authoritative lists for this endpoint.
 - *Screening*: Not present on any screening lists for this endpoint.
- ECHA 2021b
 - In an OECD Guideline 404 dermal irritation test, animals (species and sex not specified, three total) were administered topical applications of N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) (purity not specified) under semi-occlusive dressing. At unspecified time points, the erythema scores were 0.67, 0.67, and 0.33 and the edema scores were 0.67, 0.67, and 0.33. No further details were provided.
- UNEP 2005, ECHA 2021a
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A non-GLP-compliant dermal irritation test was performed with New Zealand White rabbits (6 total) administered topical applications of 0.5 mL undiluted N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (95.7% purity, warmed to 46°C to liquify) to intact and abraded skin under semi-occlusive dressing for 24 hours. A 7-day observation period followed the exposure period. At 24 and 72 hours, the mean overall irritation score was 0/8, and the authors concluded that N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was not irritating under the tested conditions (Klimisch Score 2, reliable with restrictions).

- Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A non-GLP-compliant dermal irritation test was performed with rabbits (strain not specified, 3 total) administered topical applications of undiluted N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) under occlusive dressing for 24 hours. An observation period of 120 hours followed the exposure period. The mean overall scores were 0.6/8, 1.6/8, 1.3/8, and 1/8 at 4, 24, 48, and 72 hours respectively. All signs of dermal irritation resolved within 120 hours. The authors concluded that N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was slightly irritating under the tested conditions (Klimisch Score 2, reliable with restrictions).
- Additional skin irritation tests were presented in the REACH and SIDS dossiers for N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD). However, they were reported in the REACH dossier with Klimisch Scores of 3 (not reliable) or 4 (not assignable). Therefore, ToxServices did not include the results of these studies in the current assessment.
- GHS criteria define skin irritants as chemicals that produce mean scores ≥ 1.5 for erythema and/or edema in at least 2 of 3 animals following readings at 24, 48, and 72 hours (UN 2021). As the results of the skin irritation tests for the target chemical and surrogate do not indicate skin irritation above this threshold, ToxServices did not classify N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) as a dermal irritant under GHS criteria.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of High for eye irritation/corrosivity based on an authoritative listing. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified as GHS Category 2A eye irritants (H319) by the EU (CPA 2018b). The confidence in the score is high as it is based on an authoritative A list.

- Authoritative and Screening Lists
 - *Authoritative:*
 - EU – GHS (H-Statements) – H319 – Causes serious eye irritation [Serious eye damage/eye irritation – Category 2A].
 - *Screening:*
 - GHS – Australia – H319 – Causes serious eye irritation [Serious eye damage/eye irritation – Category 2A].
- ECHA 2021b
 - In an OECD Guideline 405 eye irritation test, animals (species and sex not specified, three total) were administered ocular instillations of N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) (purity not specified). At unspecified time points, the conjunctival scores were 2, 1.67, and 2; the chemosis scores were 2, 2, and 2; the corneal opacity scores were 1, 0.33, and 0.67; and the iris scores were all zero. No further details were provided.
- UNEP 2005, ECHA 2021a
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A non-GLP-compliant ocular irritation test was performed with New Zealand White rabbits (6 total) administered ocular instillations of 0.1 mL undiluted N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (95.7% purity, warmed to 46°C to liquify) for 24 hours. An observation period of seven days followed the instillation. The animals exhibited slight discomfort immediately following instillation. At 24, 48, and 72 hours, the mean overall irritation score was 1.2/110. The irritation was characterized by slight erythema at 1, 24, and 48 hours and moderate to copious discharge at 1 and 24 hours. The ocular irritation resolved completely within 72 hours. The authors concluded that N-(1,3-dimethylbutyl)-N'-

phenyl-p-phenylenediamine (6PPD) was slightly irritating under the tested conditions (Klimisch Score 2, reliable with restrictions).

- o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A non-GLP compliant ocular irritation test was performed with rabbits (strain not specified, 3 total) administered 0.1 mL undiluted N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (purity not specified) for 24 hours. An observation period of five days followed the instillation. The mean overall irritation scores were 20.6/110, 20/110, 14.6/110, 9/110, and 4.6/110 at 1, 4, 24, 48, and 72 hours, respectively. The ocular irritation, characterized as edema and erythema at 24, 48, and 72 hours, resolved completely within 120 hours. The authors concluded that N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) was slightly irritating under the tested conditions (Klimisch Score 2, reliable with restrictions).
- o An additional eye irritation test was presented in the REACH dossier for N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD). However, it was reported in the REACH dossier with Klimisch Scores of 4 (not assignable). Therefore, ToxServices did not include the results of this study in the current assessment.

Ecotoxicity (Ecotox)

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Very High for acute aquatic toxicity based on an authoritative listing. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when acute aquatic toxicity values are ≤ 1 mg/L or they are classified as GHS Category 1 acute aquatic toxicants (H400) by the EU (CPA 2018b). The confidence in the score is high as it is based on an authoritative listing.

- Authoritative and Screening Lists
 - o *Authoritative*:
 - EU – GHS (H-Statements) – H400 – Very toxic to aquatic life [Hazardous to the aquatic environment (acute) – Category 1].
 - o *Screening*: Not present on any screening lists for this endpoint.
- Flexsys 2007, ECHA 2021b
 - o 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = 0.638 mg/L.
 - o 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) = 0.268 mg/L.
 - o 48-hour EC_{50} (*Daphnia magna*) = 1.40-1.41 mg/L.
 - o 72-hour growth rate EC_{50} (*Pseudokirchneriella subcapitata*, algae) = 1.6 mg/L.
- UNEP 2005, ECHA 2021a
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): 96-hour LC_{50} (*Oryzias latipes*, Japanese rice fish) = 0.028 mg/L (measured) (GLP-compliant, OECD Guideline 203) (Klimisch Score 1, reliable without restriction).
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): 48-hour mobility EC_{50} (*Daphnia magna*) = 0.23 mg/L (measured) (GLP-compliant, OECD Guideline 202) (Klimisch Score 1, reliable without restriction).
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): 48-hour mobility EC_{50} (*D. magna*) = 0.82 mg/L (nominal) (non-GLP-compliant, U.S. EPA 1975 Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians method) (Klimisch Score 2, reliable with restrictions).
 - o Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): 48-hour mobility EC_{50} (*D. magna*) = 0.51 mg/L (nominal) (non-GLP-compliant, U.S. EPA

1975 Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians method)
(Klimisch Score 2, reliable with restrictions).

- Test substance was N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Santoflex 13) and its degradation products.
- Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): 48-hour EC₅₀ (*D. magna*) = 0.79 mg/L (OECD Guideline 202) (Klimisch Score 4, not assignable).
- Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): An algal study presented in the REACH and SIDS dossiers identified a 96-hour chlorophyll a EC₅₀ of 0.6 mg/L in *Pseudokirchneriella subcapitata* (previously *Selenastrum capricornutum*). While this study is reported in the SIDS dossier with a Klimisch Score of 2 (reliable with restrictions), it is presented in the REACH dossier with a Klimisch Score of 3 (not reliable) due to “[s]ignificant methodological deficiencies” including the lack of exponential growth of the test organisms during the incubation period. Therefore, ToxServices did not include the results of this study in the current assessment.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Very High for chronic aquatic toxicity based on a measured chronic aquatic toxicity value of 0.004 mg/L for fish exposed to the surrogate. 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). Although chronic aquatic toxicity data were only identified for fish and not for aquatic invertebrates or algae, fish was the most sensitive trophic level for acute aquatic toxicity and the chronic fish value alone warrants the worst score for this endpoint. The confidence in the score is high as it is based on reliable measured data on a strong 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.
 - *Other*:
 - EU - GHS (H-Statements) - H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1].
 - GHS – Australia - H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1].
- ECHA 2021b
 - 72-hour growth rate NOEC (*P. subcapitata*, algae) = 0.5 mg/L.
- ECHA 2021a
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): 30-day NOEC (*O. latipes*, Japanese rice fish) = 0.004 mg/L (measured) (GLP-compliant, OECD Guideline 210) (Klimisch Score 1, reliable without restriction).

Environmental Fate (Fate)

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Very High for persistence based on an estimated half-life of 337.5 days in sediment, its predicted dominant environmental compartment. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when sediment is the dominant environmental compartment and they are recalcitrant or have

sediment half-lives > 180 days (CPA 2018b). The confidence in the score is low as it is based on modeling.

- Authoritative and Screening Lists
 - *Authoritative*: Not present on any authoritative lists for this endpoint.
 - *Screening*: Not present on any screening lists for this endpoint.
- ECHA 2021a,b
 - At 25°C in an OECD Guideline 111 test, N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) (purity not specified) has hydrolysis half-lives of 19, 4.7, and 4.3 hours at pH 4, 7, and 9, respectively. The hydrolysis products included 4-hydroxy-diphenylamine (CAS #122-37-2), p-benzoquinone (CAS #106-54-1), p-hydroquinone (CAS #123-31-9), and aniline (CAS #62-53-3).
- Flexsys 2007, ECHA 2021b
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) (purity not specified) degraded 20% after 28 days in a modified Sturm biodegradation test. No further details were provided.
- ECHA 2021a
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A GLP-compliant, OECD Guideline 301 C test (modified MITI test) was performed with activated sludge (adaption not specified) exposed to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (> 99% purity) at 100 mg/L for 28 days. At the end of the exposure period, the level of degradation was 2%. In contrast, the reference material, aniline, degraded 64% and 71% after 7 and 14 days, respectively. Therefore, the authors concluded that no biodegradation occurred under the tested condition (Klimisch Score 1, reliable without restrictions).
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A ready biodegradability test comparable to OECD Guideline 301 B was performed with adapted, activated sludge exposed to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (80.35% purity) at 30 mg/L for 32 days. At the end of the exposure period, the level of degradation was 7.2%. Therefore, the authors concluded that no biodegradation occurred under the tested condition (Klimisch Score 2, reliable with restrictions).
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): In a hydrolysis test based on OECD Guideline 111, N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (as Vulkanox 4020, > 98% purity) was performed to evaluate degradation of this chemical under environmental conditions (pH 7, presence of light, air, and algal nutrient medium). The test substance was incubated in buffered solution at 26°C or 50°C and nutrient medium (contains trace ions of essential heavy metals) at 26°C. The hydrolysis half-lives were 14 and 5 hours for the buffered solution at 26°C and 50°C, respectively, and 8 hours for the nutrient medium (Klimisch Score 2, reliable with restrictions).
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): A second OECD Guideline 301 C (modified MITI test) is presented in the REACH dossier for N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD). However, it was assigned a Klimisch Score of 3 (not reliable) due to “[s]ignificant methodological deficiencies”; therefore, ToxServices did not include the results of this study in the current assessment.
- U.S. EPA 2017
 - The BIOWIN modeling Ready Biodegradable Predictor indicates that N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) is not expected to be readily biodegradable. Fugacity

modeling (MCI method) predicts 55% will partition to sediment with a half-life of 8,100 hours (337.5 days), 41.3% will partition to soil with a half-life of 1,800 hours (75 days), and 3.59% will partition to water with a half-life of 900 hours (37.5 days) (Appendix I).

- Although the measured hydrolysis half-life is 4.7 hours at pH 7 and 25°C, fugacity modeling predicts that N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) will mostly partition into sediment and soil due to its low water solubility. In addition, the hydrolysis study only measured the rate of primary degradation and only the rates of ultimate degradation (i.e., complete mineralization) can be used to support GHS rapid degradability, unless the primary degradation products are not hazardous to the environment (i.e., classified for acute or aquatic toxicity under GHS). As the hydrolysis products p-hydroquinone (CAS #123-31-9), and aniline (CAS #62-53-3) both have harmonized GHS classifications for aquatic toxicities (Pharos 201), the hydrolysis half-lives could not be used to support rapid degradability. Therefore, ToxServices used the fugacity modeling to assign the score for this endpoint.

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of High for bioaccumulation based on measured BCFs of 1,500-1,700 for the surrogate N-(1-methylheptyl)-N'-phenylbenzene-1,4-diamine. GreenScreen® criteria classify chemicals as a High hazard for bioaccumulation when BCFs are > 1,000 to 5,000 (CPA 2018b). The confidence in the score is high as it is based on measured data for a strong 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.
- U.S. EPA 2017
 - BCFBAF predicts a BCF of 274.3 L/kg wet-wt using the regression based model based on a measured log K_{ow} of 4.20, and a BCF of 432.7 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix I).
- UNEP 2005
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) is not stable in water (see persistence section above). Therefore, it is not likely to bioaccumulate despite a calculated BCF of 801. The degradation products 1,3-dimethylbutylamine, N-phenyl-p-benzoquinone monoamine, and 4-hydroxydiphenylamine have experimentally obtained BCFs of ≤ 30, indicating that they are not likely to bioaccumulate in aquatic biota.
- ECHA 2021a
 - Surrogate: N-(1-Methylheptyl)-N'-phenylbenzene-1,4-diamine (CAS #15233-47-3): A GLP-compliant, OECD Guideline 305 E bioaccumulation test was performed with carp (*Cyprinus carpio*) exposed to N-(1-methylheptyl)-N'-phenylbenzene-1,4-diamine (purity not specified, not radiolabeled) at nominal concentrations of 1 or 10 µg/L for 28 days. The steady state BCFs on the basis of normalized lipid fractions were 1,700 and 1,500 for the 1 and 10 µg/L solutions, respectively.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): L

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen®

criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score was high as it is based on measured surrogate data for explosivity.

- Authoritative and Screening Lists
 - *Authoritative*: Not present on any authoritative lists for this endpoint.
 - *Screening*: Not present on any screening lists for this endpoint.
- Flexsys 2007
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) has reactivity ratings of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives") and NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water").
- ECHA 2021
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (purity not specified) was not explosive in an EU Method A.14 test. No further details were provided.
 - Surrogate: N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) (CAS #793-24-8): N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) does not contain functional groups associated with oxidizing properties.
- Based on the above information, ToxServices did not classify N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) as a reactive chemical under GHS criteria (UN 2021).

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

N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable chemical under GHS criteria. GreenScreen[®] criteria classify chemicals as a Low hazard for flammability when no GHS classification is available (CPA 2018b). The confidence in the score was low due to the limited level of detail available for the key study.

- 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
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) (purity not specified) has a flash point of 196°C as identified in an open cup test.
 - N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI) (purity not specified) has an auto-ignition temperature of 485°C.
- As N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI) has a flash point greater than 93°C, ToxServices did not classify it as a flammable liquid under GHS criteria (UN 2021).

Use of New Approach Methodologies (NAMs)¹³ in the Assessment, Including Uncertainty Analyses of Input and Output

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

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

As shown in Table 5, Type I (input data) uncertainties in N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI)'s NAMs dataset include lack of experimental data for respiratory sensitization along with a lack of validated test method for respiratory sensitization. N-1,3-Dimethyl butyl-N'-phenyl quinone diamine (6QDI)'s Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of OECD Toolbox in identifying structural alerts without defining the applicability domain, the uncertain relevance of the EDSP Tox 21 screening assays and *in silico* modeling of endocrine receptor binding due to lack of consideration of toxicokinetic factors including metabolism, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI)'s type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	Respiratory sensitization: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	Carcinogenicity: Identification of morphologically transformed colonies in the <i>in vitro</i> mammalian cell transformation assay could be subjective. The mechanism leading to cell transformations is not fully understood. The test does not inform <i>in vivo</i> potency, species-specificity or tissue-specificity of cell transformations, and is being validated for mono-constituent substances only ¹⁴ .

¹³ 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).

¹⁴ <https://www.oecd.org/env/ehs/testing/Guidance-Document-on-the-in-vitro-Syrian-Hamster-Embryo-Cell-Transformation-Assay.pdf>

	Genotoxicity: The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic <i>in vivo</i> conditions¹⁵. 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 <i>in vivo</i> metabolism (i.e. the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).¹⁶ The <i>in vitro</i> 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 <i>in vivo</i> metabolism¹⁷. Endocrine activity: ToxCast models don't define applicability domain; the <i>in vivo</i> relevance of EDSP Tox 21 screening assays is unknown due to lack of consideration of metabolism and other toxicokinetic factors. 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 (<i>in silico</i> modeling/ <i>in vitro</i> biological profiling/frameworks)
Carcinogenicity	N	
Mutagenicity	Y	<i>In vitro</i> data: Bacterial reverse mutation assay/ <i>in vitro</i> gene mutation assay/ <i>in vitro</i> chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	<i>In vitro</i> high throughput data: EDSP Tox 21 screening assays/ToxCast models/ Danish QSAR/VEGA
Acute mammalian toxicity	N	

¹⁵ <https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427>

¹⁶ <https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE>

¹⁷ <https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352>

Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	<i>In silico</i> modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	<i>In silico</i> modeling: EPI Suite™ Non-animal testing: modified Sturm Biodegradation test
Bioaccumulation	Y	<i>In silico</i> 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 N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING 			GreenScreen® Score Inspector																							
			Table 1: Hazard Table																							
			Group I Human					Group II and II* Human										Ecotox		Fate		Physical				
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization *	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability				
Table 2: Chemical Details								S	R *	S	R *	*	*													
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F				
No	N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine	52870-46-9	L	L	H	M	M	M	M	M	M	DG	H	DG	L	H	vH	vH	vH	H	L	L				
Table 3: Hazard Summary Table										Table 4				Table 6												
Benchmark		a	b	c	d	e	f	g	Chemical Name		Preliminary GreenScreen® Benchmark Score		Chemical Name		Final GreenScreen® Benchmark Score											
1		Yes	No	Yes	No	Yes			N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine		1		N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine		1											
2		STOP							Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score																	
3		STOP																								
4		STOP																								
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 N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)



52870-46-9
N-(1,3-dimethylbutyl)-N'-(phenyl)-1,4-benzoquinonediimine
ALSO CALLED Benzenamine, N-(4-((1,3-dimethylbutyl)imino)-2,5-cyclohexadien-1-ylidene)-
View all synonyms (1)

[Share Profile](#)

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[Properties](#)
[Functional Uses](#)
[Resources](#)

[All Hazards View](#)

☐ Show PubMed Results

[Request Assessment](#)

[Add to Comparison](#)

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

Hazard Lists

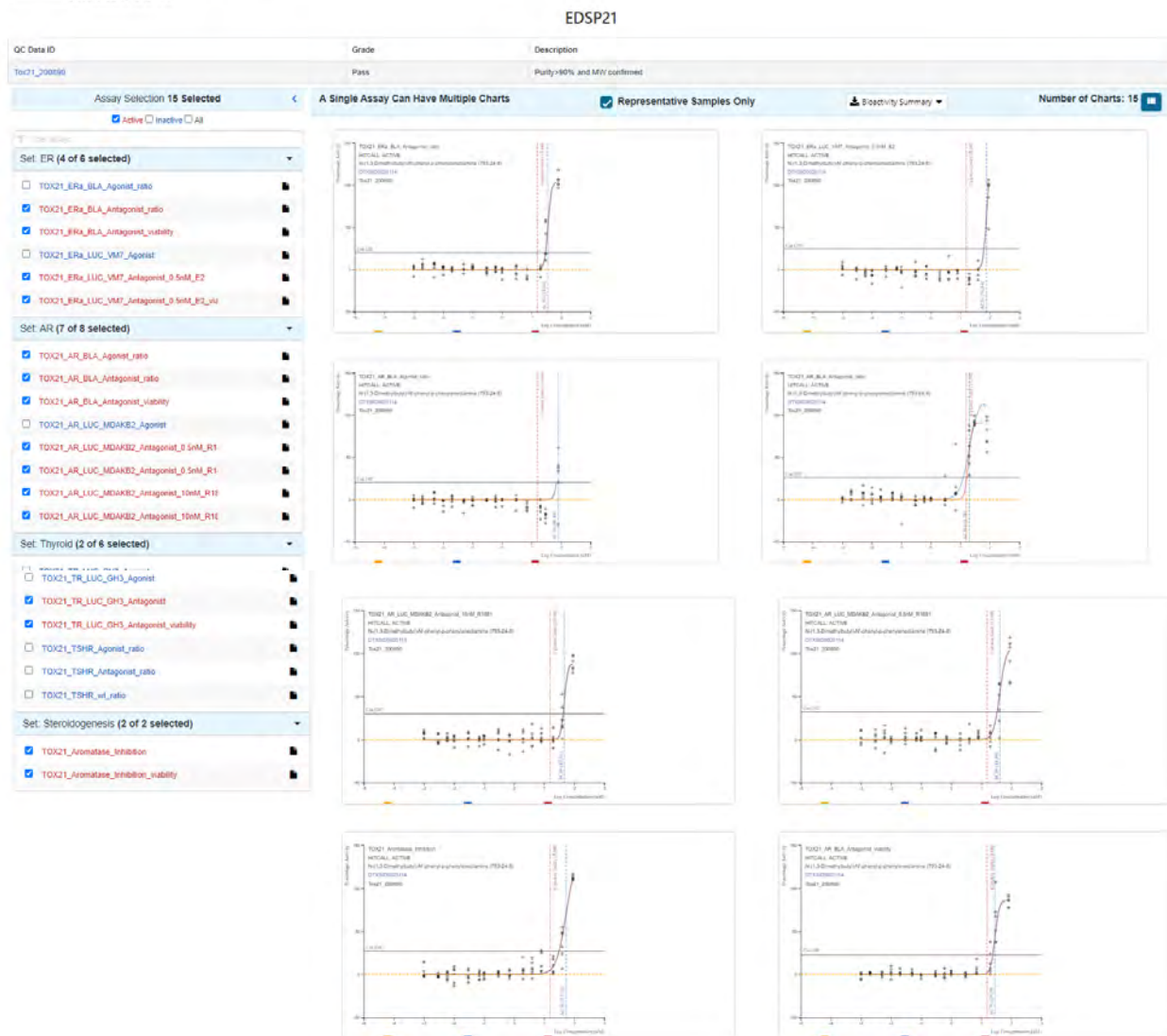
[Download Lists](#)

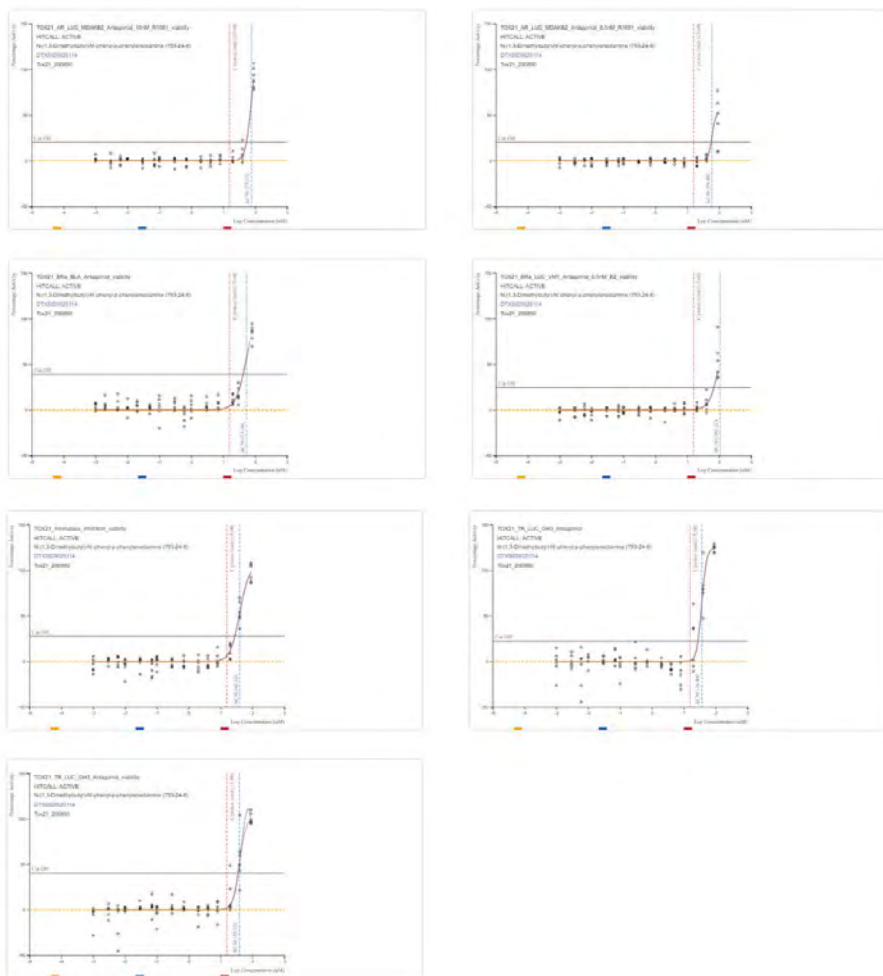
ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Eye Irritation/Corrosivity	H	LT-UNK	EU - GHS (H-Statements)	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	+1
	H	LT-UNK	GHS - Australia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
Acute Aquatic Toxicity	VH	LT-UNK	EU - GHS (H-Statements)	H400 - Very toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 1]	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-P1	EU - GHS (H-Statements)	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	+1
	U	LT-P1	GHS - Australia	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	

APPENDIX D: CompTox EDSP21 Results for the Surrogate N-(1,3-Dimethylbutyl)-N'-Phenyl-p-Phenylenediamine (6PPD) (CAS #793-24-8)

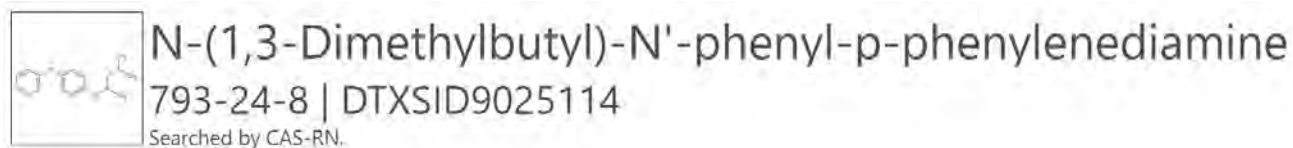


N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine
 793-24-8 | DTXSID9025114
 Searched by CAS-RN1





APPENDIX E: ToxCast Model Predictions for the Surrogate N-(1,3-Dimethylbutyl)-N'-Phenyl-p-Phenylenediamine (6PPD) (CAS #793-24-8)



ToxCast: Models ToxCast Model Predictions

[Download ToxCast Model Predictions](#)

Model	Receptor	Agonist	Antagonist	Binding
i ToxCast Pathway Model (AUC)	Androgen	-	-	-
i ToxCast Pathway Model (AUC)	Estrogen	-	-	-
i COMPARA (Consensus)	Androgen	Inactive	Active	Inactive
i CERAPP Potency Level (From Literature)	Estrogen	Inactive (Inactive)	Active (Very weak)	Active (Very weak)
i CERAPP Potency Level (Consensus)	Estrogen	Inactive (Inactive)	Inactive (Inactive)	Inactive (Inactive)

APPENDIX F: VEGA Endocrine Activity Results for N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)



Estrogen Receptor Relative Binding Affinity model (IRFMN)

page 1



1. Prediction Summary

Prediction for compound Molecule 0

	Prediction: Reliability: Prediction is Active, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues: - only moderately similar compounds with known experimental value in the training set have been found - accuracy of prediction for similar molecules found in the training set is not optimal - similar molecules found in the training set have experimental values that disagree with the predicted value - some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (3 infrequent fragments found)
--	---

Compound: Molecule 0

Compound SMILES: N(c1ccccc1)=C2C=CC(=NC(C)CC(C)C)C=C2

Experimental value: -

Predicted activity: Active

Classification tree final node: 18

Reliability: the predicted compound is outside the Applicability Domain of the model

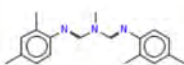
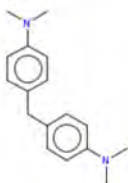
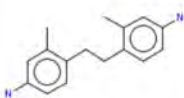
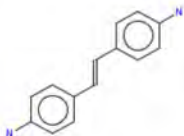
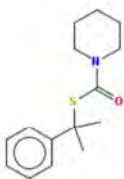
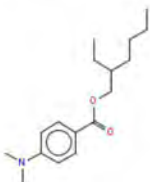
Remarks:

none

3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values



	Compound #1 CAS: 33089-61-1 Dataset id: 604 (Training set) SMILES: <chem>N(=CN(C=Nc1ccc(cc1C)C)C)c2ccc(cc2C)C</chem> Similarity: 0.747 Experimental value: Inactive Predicted value: Inactive
	Compound #2 CAS: 101-61-1 Dataset id: 693 (Training set) SMILES: <chem>c1cc(ccc1N(C)C)Cc2ccc(cc2)N(C)C</chem> Similarity: 0.741 Experimental value: Inactive Predicted value: Active
	Compound #3 CAS: 22856-62-8 Dataset id: 523 (Training set) SMILES: <chem>Nc1ccc(cc1C)CCc2ccc(N)cc2C</chem> Similarity: 0.739 Experimental value: Active Predicted value: Active
	Compound #4 CAS: 54760-75-7 Dataset id: 541 (Training set) SMILES: <chem>Nc1ccc(cc1C)C=Cc2ccc(N)cc2</chem> Similarity: 0.734 Experimental value: Inactive Predicted value: Inactive
	Compound #5 CAS: 61432-55-1 Dataset id: 597 (Training set) SMILES: <chem>O=C(N1CCCCC1)SC(c2ccccc2)(C)C</chem> Similarity: 0.732 Experimental value: Inactive Predicted value: Inactive
	Compound #6 CAS: 21245-02-3 Dataset id: 371 (Training set) SMILES: <chem>O=C(OCC(CC)CCCC)c1ccc(cc1)N(C)C</chem> Similarity: 0.716 Experimental value: Inactive Predicted value: Inactive

3.2 Applicability Domain: Measured Applicability Domain Scores



Global AD Index

AD index = 0

Explanation: the predicted compound is outside the Applicability Domain of the model.



Similar molecules with known experimental value

Similarity index = 0.744

Explanation: only moderately similar compounds with known experimental value in the training set have been found.



Accuracy of prediction for similar molecules

Accuracy index = 0.503

Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.



Concordance for similar molecules

Concordance index = 0

Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.



Model's descriptors range check

Descriptors range check = True

Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.



Atom Centered Fragments similarity check

ACF index = 0.7

Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (3 infrequent fragments found).

Symbols explanation:



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



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



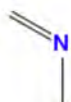
The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning: Relevant Chemical Fragments and Moieties

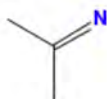


(Molecule 0) Reasoning on rare and missing Atom Centered Fragments.

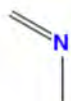
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:



Fragment defined by the SMILES: N(=C)C
The fragment has less than 3 occurrences in the model's training set



Fragment defined by the SMILES: N=C(C)C
The fragment has less than 3 occurrences in the model's training set



Fragment defined by the SMILES: N(=C)c
The fragment has less than 3 occurrences in the model's training set



1. Prediction Summary

Prediction for compound Molecule 0

	Prediction: Reliability: Prediction is Possible NON-active, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections. Anyway some issues could be not optimal: - only moderately similar compounds with known experimental value in the training set have been found The following relevant fragments have been found: ER possible non-activity alert no. 4
--	---

Compound: Molecule 0

Compound SMILES: N(c1ccccc1)=C2C=CC(=NC(C)CC(C)C)C=C2

Experimental value: -

Predicted ER-mediated effect: Possible NON-active

No. alerts for activity: 0

No. alerts for possible activity: 0

No. alerts for non-activity: 0

No. alerts for possible non-activity: 1

Structural alerts: ER possible non-activity alert no. 4

Reliability: the predicted compound is into the Applicability Domain of the model

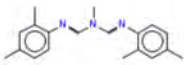
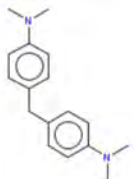
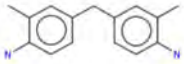
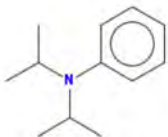
Remarks:

none

3.1 Applicability Domain:

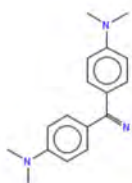
Similar Compounds, with Predicted and Experimental Values



	Compound #1 CAS: N.A. Dataset id: 1227 (Training set) SMILES: <chem>N(=CN(C=Nc1ccc(cc1C)C)C)c2ccc(cc2C)C</chem> Similarity: 0.747 Experimental value: NON-active Predicted value: Possible NON-active Alerts (found also in the target): ER possible non-activity alert no. 4 Alerts (not found in the target): ER possible non-activity alert no. 7
	Compound #2 CAS: N.A. Dataset id: 358 (Training set) SMILES: <chem>c1cc(ccc1N(C)C)Cc2ccc(cc2)N(C)C</chem> Similarity: 0.741 Experimental value: NON-active Predicted value: Possible NON-active Alerts (found also in the target): ER possible non-activity alert no. 4 Alerts (not found in the target): ER possible non-activity alert no. 7
	Compound #3 CAS: N.A. Dataset id: 854 (Training set) SMILES: <chem>Nc1ccc(cc1C)Cc2ccc(N)c(c2)C</chem> Similarity: 0.73 Experimental value: NON-active Predicted value: Possible NON-active Alerts (found also in the target): ER possible non-activity alert no. 4 Alerts (not found in the target): ER possible non-activity alert no. 7
	Compound #4 CAS: N.A. Dataset id: 1039 (Training set) SMILES: <chem>c1ccc(cc1)N(C(C)C)C(C)C</chem> Similarity: 0.727 Experimental value: NON-active Predicted value: NON-active Alerts (found also in the target): ER possible non-activity alert no. 4 Alerts (not found in the target): ER non-activity alert no. 4

3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values



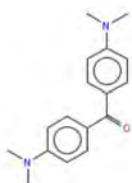
Compound #5

CAS: N.A.
Dataset id: 744 (Training set)
SMILES: N=C(c1ccc(cc1)N(C)C)c2ccc(cc2)N(C)C
Similarity: 0.72

Experimental value: NON-active
Predicted value: Possible NON-active

Alerts (found also in the target): ER possible non-activity alert no. 4

Alerts (not found in the target): ER possible non-activity alert no. 7



Compound #6

CAS: N.A.
Dataset id: 231 (Training set)
SMILES: O=C(c1ccc(cc1)N(C)C)c2ccc(cc2)N(C)C
Similarity: 0.718

Experimental value: NON-active
Predicted value: Possible NON-active

Alerts (found also in the target): ER possible non-activity alert no. 4

Alerts (not found in the target): ER possible non-activity alert no. 7; ER possible non-activity alert no. 9

3.2 Applicability Domain: Measured Applicability Domain Scores

**Global AD Index**

AD index = 0.86

Explanation: the predicted compound is into the Applicability Domain of the model.

**Similar molecules with known experimental value**

Similarity index = 0.739

Explanation: only moderately similar compounds with known experimental value in the training set have been found.

**Accuracy of prediction for similar molecules**

Accuracy index = 1

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

**Concordance for similar molecules**

Concordance index = 1

Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

**Atom Centered Fragments similarity check**

ACF index = 1

Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:



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



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



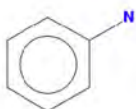
The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning: Relevant Chemical Fragments and Moieties



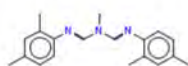
(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: ER possible non-activity alert no. 4



Fragment related to possible non-activity for ER-mediated effect, defined by the SMARTS: Nc1ccccc1

Following, the most similar compounds from the model's dataset having the same fragment.

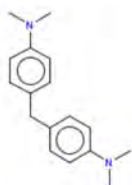


CAS: N.A.
Dataset id: 1227 (Training set)
SMILES: N(=CN(C=Nc1ccc(cc1C)C)C)c2ccc(cc2C)C
Similarity: 0.747

Experimental value: NON-active
Predicted value: Possible NON-active

Alerts (found also in the target): ER possible non-activity alert no. 4

Alerts (not found in the target): ER possible non-activity alert no. 7

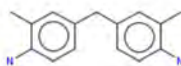


CAS: N.A.
Dataset id: 358 (Training set)
SMILES: c1cc(ccc1N(C)C)Cc2ccc(cc2)N(C)C
Similarity: 0.741

Experimental value: NON-active
Predicted value: Possible NON-active

Alerts (found also in the target): ER possible non-activity alert no. 4

Alerts (not found in the target): ER possible non-activity alert no. 7



CAS: N.A.
Dataset id: 854 (Training set)
SMILES: Nc1ccc(cc1C)Cc2ccc(N)c(c2)C
Similarity: 0.73

Experimental value: NON-active
Predicted value: Possible NON-active

Alerts (found also in the target): ER possible non-activity alert no. 4

Alerts (not found in the target): ER possible non-activity alert no. 7



1. Prediction Summary

Prediction for compound Molecule 0

	Prediction: Reliability: Prediction is NON-active, but the result shows some critical aspects, which require to be checked: - only moderately similar compounds with known experimental value in the training set have been found - accuracy of prediction for similar molecules found in the training set is not adequate The following relevant fragments have been found: ER alert no. 111, inactive
--	---

Compound: Molecule 0

Compound SMILES: N(c1ccccc1)=C2C=CC(=NC(C)CC(C)C)C=C2

Experimental value: -

Predicted AR binding activity: NON-active

No. alerts for binding activity: 0

No. alerts for non-binding activity: 1

Structural alerts: ER alert no. 111, inactive

Reliability: the predicted compound could be out of the Applicability Domain of the model

Remarks:

none

3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values



	Compound #1 CAS: 548-62-9 Dataset id: 208 (Training set) SMILES: <chem>C[N+](C)=C1C=CC(C=C1)=C(c1ccc(cc1)N(C)C)c1ccc(cc1)N(C)C</chem> Similarity: 0.75 Experimental value: NON-active Predicted value: Active Alerts (not found in the target): ER alert no. 142, active
	Compound #2 CAS: 33089-61-1 Dataset id: 1564 (Training set) SMILES: <chem>CN(C=Nc1ccc(C)cc1C)C=Nc1ccc(C)cc1C</chem> Similarity: 0.747 Experimental value: NON-active Predicted value: NON-active Alerts (not found in the target): ER alert no. 53, inactive
	Compound #3 CAS: 101-61-1 Dataset id: 390 (Training set) SMILES: <chem>CN(C)c1ccc(Cc2ccc(cc2)N(C)C)cc1</chem> Similarity: 0.741 Experimental value: NON-active Predicted value: NON-active
	Compound #4 CAS: 35256-85-0 Dataset id: 1284 (Training set) SMILES: <chem>CC(C)(C)C(=O)N(Cc1ccccc1)C(C)C</chem> Similarity: 0.73 Experimental value: NON-active Predicted value: NON-active Alerts (not found in the target): ER alert no. 77, inactive; ER alert no. 140, active
	Compound #5 CAS: 838-88-0 Dataset id: 1551 (Training set) SMILES: <chem>Cc1cc(Cc2cc(C)c(N)cc2)ccc1N</chem> Similarity: 0.73 Experimental value: NON-active Predicted value: NON-active

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



	Compound #6
	CAS: 4107-98-6
	Dataset id: 1321 (Training set)
	SMILES: <chem>CC(C)N(C(C)C)c1ccccc1</chem>
	Similarity: 0.727
Experimental value: NON-active	
Predicted value: NON-active	

3.2 Applicability Domain: Measured Applicability Domain Scores



	Global AD Index AD index = 0.727 Explanation: the predicted compound could be out of the Applicability Domain of the model.
	Similar molecules with known experimental value Similarity index = 0.748 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
	Accuracy of prediction for similar molecules Accuracy index = 0.499 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
	Concordance for similar molecules Concordance index = 1 Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.
	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

4.1 Reasoning: Relevant Chemical Fragments and Moieties

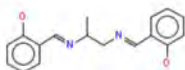


(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: ER alert no. 111, inactive

Fragment related to ER inactivity (high reliability), defined by the SMARTS: CCN=C

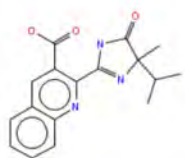
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 94-91-7
Dataset id: 1236 (Training set)
SMILES: CC(CN=Cc1ccccc1O)N=Cc1ccccc1O
Similarity: 0.718

Experimental value: NON-active
Predicted value: NON-active

Alerts (found also in the target): ER alert no. 111, inactive

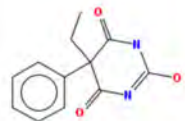


CAS: 81335-37-7
Dataset id: 709 (Training set)
SMILES: CC(C)C1(C)N=C(NC1=O)c1[n]c2ccccc2cc1C(=O)O
Similarity: 0.668

Experimental value: NON-active
Predicted value: NON-active

Alerts (found also in the target): ER alert no. 111, inactive

Alerts (not found in the target): ER alert no. 21, inactive; ER alert no. 35, inactive; ER alert no. 84, inactive



CAS: 57-30-7
Dataset id: 426 (Training set)
SMILES: CCC1(c2ccccc2)C(=O)NC(O)=NC1=O
Similarity: 0.665

Experimental value: NON-active
Predicted value: NON-active

Alerts (found also in the target): ER alert no. 111, inactive

Alerts (not found in the target): ER alert no. 116, inactive; ER alert no. 143, active

**APPENDIX G: Danish QSAR Endocrine Activity Results for N-1,3-Dimethyl Butyl-N'-Phenyl
 Quinone Diamine (6QDI) (CAS #52870-46-9)**

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human <i>in vitro</i>)		NEG_IN	INC_OUT	NEG_IN	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human <i>in vitro</i>)		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
Estrogen Receptor α Activation (Human <i>in vitro</i>)		INC_OUT	INC_OUT	NEG_OUT	NEG_OUT
Estrogen Receptor Activation, CERAPP data (<i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Inhibition (Human <i>in vitro</i>)		INC_OUT	INC_OUT	NEG_OUT	NEG_OUT
Androgen Receptor Binding, CoMPARA data (<i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Inhibition, CoMPARA data (<i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Activation, CoMPARA data (<i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat <i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat <i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Thyroid Receptor α Binding (Human <i>in vitro</i>)					
- mg/L			42610.63	1792.083	27.34752
- μ M			159955.8	6727.289	102.6597
- Positive for $IC_{50} \leq 10 \mu$ M					
- Positive for $IC_{50} \leq 100 \mu$ M					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human <i>in vitro</i>)					
- mg/L			8620.217	16.41526	22.76764
- μ M			32359.38	61.62117	85.46731
- Positive for $IC_{50} \leq 10 \mu$ M					
- Positive for $IC_{50} \leq 100 \mu$ M					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human <i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human <i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Pregnane X Receptor (PXR) Binding (Human <i>in vitro</i>)	N/A	POS_IN	INC_OUT	POS_IN	POS_IN
Pregnane X Receptor (PXR) Binding (Human <i>in vitro</i>) NEW		N/A	N/A	POS_IN	N/A
Pregnane X Receptor (PXR) Activation (Human <i>in vitro</i>)		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Pregnane X Receptor (PXR) Activation (Rat <i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (<i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (<i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (<i>in vitro</i>)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (<i>in vitro</i>)		N/A	N/A	NEG_OUT	N/A
	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
CYP3A4 Induction (Human <i>in vitro</i>)		N/A	N/A	INC_OUT	N/A

DTU-developed models

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, without OH or NH2 group
- metabolites from <i>in vivo</i> Rat metabolism simulator only	Strong binder, OH group
- metabolites from Rat liver S9 metabolism simulator only	Strong binder, OH group
rER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from <i>in vivo</i> Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

APPENDIX H: OECD Toolbox Respiratory Sensitization Results for N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) (CAS #52870-46-9)

Filter endpoint tree...

Structure

+ Structure info

+ Parameters

+ Physical Chemical Properties

+ Environmental Fate and Transport

+ Ecotoxicological Information

+ Human Health Hazards

- Profiling

- Endpoint Specific**
 - Respiratory sensitisation**

1 [target]

No alert found

**APPENDIX I: EPI Suite™ Modeling Results for N-1,3-Dimethyl Butyl-N' -Phenyl Quinone
Diamine (6QDI) (CAS #52870-46-9)**

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

CAS Number: 52870-46-9

SMILES: C1(=NC(C)CC(C)C)C=CC(=Nc2ccccc2)C=C1

CHEM:

MOL FOR: C18 H22 N2

MOL WT: 266.39

----- EPI SUMMARY (v4.11) -----

Physical Property Inputs:

Log Kow (octanol-water): 4.20

Boiling Point (deg C): 300.00

Melting Point (deg C): -10.00

Vapor Pressure (mm Hg): 7.5E-006

Water Solubility (mg/L): -----

Henry LC (atm-m3/mole): -----

Log Octanol-Water Partition Coef (SRC):

Log Kow (KOWWIN v1.69 estimate) = 5.86

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):

Boiling Pt (deg C): 352.87 (Adapted Stein & Brown method)

Melting Pt (deg C): 64.21 (Mean or Weighted MP)

VP (mm Hg, 25 deg C): 0.00195 (Modified Grain method)

VP (Pa, 25 deg C): 0.26 (Modified Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):

Water Solubility at 25 deg C (mg/L): 17.79

log Kow used: 4.20 (user entered)

melt pt used: -10.00 deg C

Water Sol Estimate from Fragments:

Wat Sol (v1.01 est) = 0.040812 mg/L

ECOSAR Class Program (ECOSAR v1.11):

Class(es) found:

Schiff Bases-Azomethine

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

Bond Method: 4.66E-004 atm-m3/mole (4.72E+001 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: 1.478E-007 atm-m3/mole (1.497E-002 Pa-m3/mole)

VP: 7.5E-006 mm Hg (source: User-Entered)

WS: 17.8 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:

Log Kow used: 4.20 (user entered)

Log Kaw used: -1.720 (HenryWin est)

Log Koa (KOAWIN v1.10 estimate): 5.920

Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):

Biowin1 (Linear Model) : 0.7488

Biowin2 (Non-Linear Model) : 0.7360

Expert Survey Biodegradation Results:

Biowin3 (Ultimate Survey Model): 2.6325 (weeks-months)

Biowin4 (Primary Survey Model) : 3.4683 (days-weeks)

MITI Biodegradation Probability:

Biowin5 (MITI Linear Model) : 0.1285

Biowin6 (MITI Non-Linear Model): 0.0574

Anaerobic Biodegradation Probability:

Biowin7 (Anaerobic Linear Model): -0.2614

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): 0.001 Pa (7.5E-006 mm Hg)

Log Koa (Koawin est): 5.920

Kp (particle/gas partition coef. (m³/ug)):

Mackay model : 0.003

Octanol/air (Koa) model: 2.04E-007

Fraction sorbed to airborne particulates (phi):

Junge-Pankow model : 0.0978

Mackay model : 0.194

Octanol/air (Koa) model: 1.63E-005

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant = 121.6262 E-12 cm³/molecule-sec

Half-Life = 0.088 Days (12-hr day; 1.5E6 OH/cm³)

Half-Life = 1.055 Hrs

Ozone Reaction:

OVERALL Ozone Rate Constant = 0.350000 E-17 cm³/molecule-sec

Half-Life = 3.274 Days (at 7E11 mol/cm³)

Half-Life = 78.583 Hrs

Fraction sorbed to airborne particulates (phi):

0.146 (Junge-Pankow, Mackay avg)

1.63E-005 (Koa method)

Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):

Koc : 4.173E+005 L/kg (MCI method)
 Log Koc: 5.620 (MCI method)
 Koc : 4413 L/kg (Kow method)
 Log Koc: 3.645 (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 = 2.438 (BCF = 274.3 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.1441 days (HL = 1.393 days)
Log BCF Arnot-Gobas method (upper trophic) = 2.636 (BCF = 432.7)
Log BAF Arnot-Gobas method (upper trophic) = 2.637 (BAF = 433.4)
log Kow used: 4.20 (user entered)

Volatilization from Water:

Henry LC: 0.000466 atm-m³/mole (estimated by Bond SAR Method)
 Half-Life from Model River: 3.716 hours
 Half-Life from Model Lake : 177.4 hours (7.391 days)

Removal In Wastewater Treatment:

Total removal: 47.99 percent
 Total biodegradation: 0.36 percent
 Total sludge adsorption: 37.25 percent
 Total to Air: 10.38 percent
 (using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0553	2.06	1000
Water	3.59	900	1000
Soil	41.3	1.8e+003	1000
Sediment	55	8.1e+003	0
Persistence Time: 2.12e+003 hr			

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0553	2.06	1000
Water	3.59	900	1000
water	(2.21)		
biota	(0.00175)		
suspended sediment	(1.38)		
Soil	41.3	1.8e+003	1000
Sediment	55	8.1e+003	0
Persistence Time: 2.12e+003 hr			

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.146	2.06	1000
Water	9.96	900	1000
water	(9.85)		
biota	(0.00781)		
suspended sediment	(0.096)		
Soil	86.2	1.8e+003	1000
Sediment	3.75	8.1e+003	0
Persistence Time: 981 hr			

APPENDIX J: Change in Benchmark Score

Table 6 provides a summary of changes to the GreenScreen® Benchmark™ for N-1,3-dimethyl butyl-N'-phenyl quinone diamine (6QDI). This GreenScreen® has undergone one round of update and the benchmark score remains the same.

Table 6: Change in GreenScreen® Benchmark™ for N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI)			
Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
October 15, 2021	BM-1	v. 1.4	New assessment
November 8, 2021	BM-1	v. 1.4	Updated hazard score for bioaccumulation.

Licensed GreenScreen® Profilers

N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) GreenScreen® Evaluation Prepared by:

SIGNATURE
BLOCK

Zach Guerrette, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC

N-1,3-Dimethyl Butyl-N'-Phenyl Quinone Diamine (6QDI) GreenScreen® Evaluation QC'd by:

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