DIPROPYL HEPTYL PHTHALATE (DPHP)

(CAS #53306-54-0)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: March 17, 2022

Expiration Date: March 17, 2027

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TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for DPHP (CAS #53306-54-0)

Dipropyl heptyl phthalate (DPHP) is an ortho phthalate with a C7 branched backbone with a propyl side chain. It belongs to the High Molecular Weight Phthalate Esters (HMWPE) group and is primarily used as a plasticizer.

DPHP is a clear, colorless, viscous liquid at room temperature that is insoluble in water. It is not volatile, reactive or a flammable liquid.

DPHP was assigned a **GreenScreen Benchmark™ Score of U** ("Unspecified Due to Insufficient Data")**.** Prior to the data gap analysis, it was assigned a preliminary Benchmark score of 2 ("Use but Search for Safer Substitutes"). This preliminary score is based on the following hazard score:

- Benchmark 2e
    - Moderate Group I Human Toxicity (Developmental toxicity-D, and endocrine activity-D)

Data gaps (DG) exist for carcinogenicity (C) and neurotoxicity (repeated dose-Nr*). As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), DPHP does not meet requirements for a GreenScreen® Benchmark Score of 2 due to the hazard data gaps. Therefore, it was assigned a GreenScreen® Benchmark Score of U. In a worst-case scenario, if DPHP were assigned a High score for the data gap C, it would be categorized as a Benchmark 1 Chemical.

The GreenScreen® Benchmark Score for DPHP has changed over time. ToxServices's original GreenScreen® assessment was performed in 2012 under version 1.2 criteria and ToxServices assigned a Benchmark U (BM-U) score. In 2018, ToxServices changed the BM-U score to a BM-2 with a version 1.3 update. Most recently, ToxServices changed the GreenScreen® benchmark score to a BM-U due to reclassification of the carcinogenicity endpoint from *M* (low confidence) to DG following a weight of evidence evaluation of this chemical's carcinogenicity dataset.

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

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

Type I (input data) uncertainties in DPHP's NAMs dataset include the absence of experimental data for respiratory sensitization, and environmental partitioning, and lack of established test methods for respiratory sensitization. DPHP's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays to mimic *in vivo* metabolic conditions, lack of defined applicability domains for OECD Toolbox and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of the type I and type II errors can be alleviated by the use of genotoxicity test batteries in combination with *in vivo* data, and ECHA's decision framework to evaluate respiratory sensitization.

GreenScreen® Hazard Summary Table for DPHP

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*	*	*								
DG	**L**	**L**	*M*	*M*	**L**	**L**	*M*	*L*	DG	**L**	*L*	**L**	**L**	**L**	**L**	**vL**	**vL**	*L*	**L**

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

GreenScreen® Chemical Assessment for DPHP (CAS #53306-54-0)

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

GreenScreen™ Assessment (v.1.2) Prepared By
Name: Chris Schlosser, M.F.S.

Title: Associate Toxicologist
Organization: ToxServices LLC
Date: December 19, 2011
Revised: February 10, 2012
Revised: May 9, 2012

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Organization: ToxServices LLC
Date: February 13, 2012; May 30, 2012

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Organization: ToxServices LLC
Date: January 24, 2018
Expiration Date[2]:February 9, 2021

Quality Control Performed By:
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Title: Senior Toxicologist
Organization: ToxServices LLC
Date: February 9, 2018

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Mouna Zachary, Ph.D.
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Date: March 15, 2022
Expiration Date: March 15, 2027[3]

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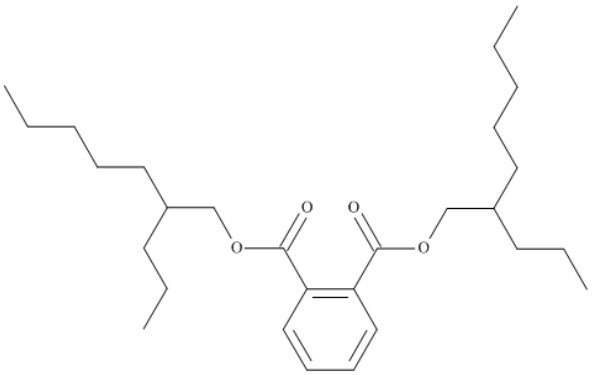
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: March 17, 2022

Chemical Name: Dipropyl heptyl phthalate (DPHP)

CAS Number: 53306-54-0

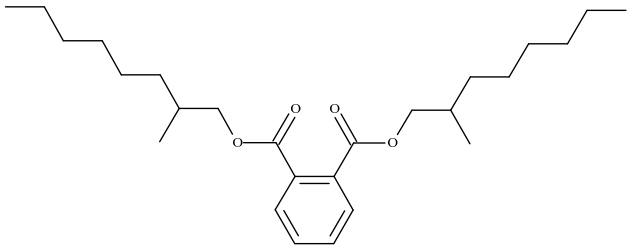
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire three years from the date of completion.
[3] Assessments expire five years from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

Chemical Structure(s):

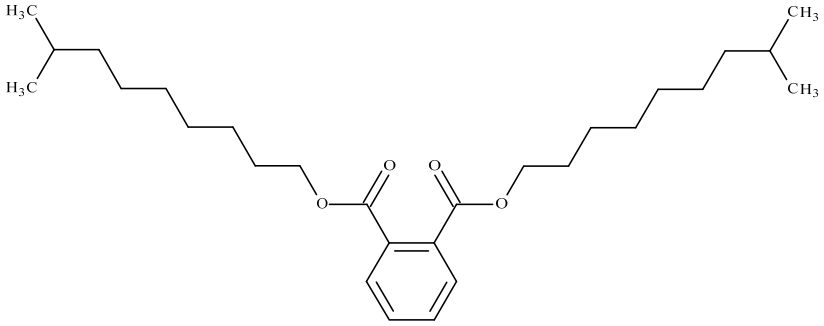


Also called:
1,2-Benzenedicarboxylic acid, 1,2-bis(2-propylheptyl) ester; Bis(2-propylheptyl) phthalate; Bis-(2-propylheptyl) phthalate; EINECS 258-469-4 (ChemIDplus 2022).

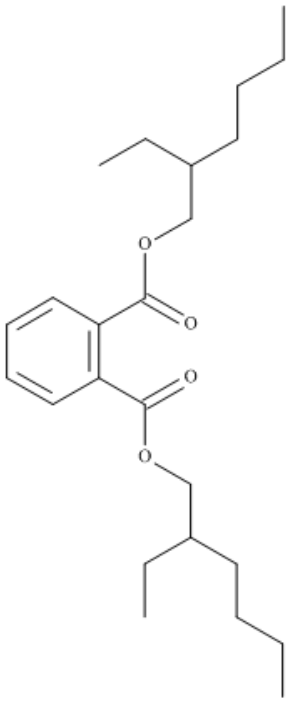
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
A relatively complete dataset was available for DPHP, with the exception of the carcinogenicity endpoint. To support the evaluation of carcinogenicity, mutagenicity, aquatic toxicity, and bioaccumulation, diisononyl phthalate (DINP, CAS #28553-12-0), di-(2-ethylhexyl)phthalate (DEHP, CAS #117-81-7), and diisodecylphthalate (DIDP, CAS #26761-40-0, 68515-49-1) are used as surrogates. All these chemcials have been used as read-across chemicals by the authors of the United States Consumer Product Safety Commission (U.S. CPSC), MAK and the REACH dossier for DPHP (MAK 2017, CPSC 2019, ECHA 2022a). All three surrogates and the target chemical are alkyl esters of phthalic acid; DIDP and DINP are substances in the long chain group (>=C7) while DEHP is in the medium chain group (C3-C7 category). Available studies with phthalic acid esters showed that the size of the molecules plays an important role in their toxicities behavior. Therefore, DEHP is considered as a weak surrogate.



Surrogate: DINP (CAS #28553-12-0)



Surrogate: DIDP (CAS #26761-40-0, 68515-49-1)



Surrogate: DEHP (CAS #117-81-7)

Identify Applications/Functional Uses: (MAK 2017, CPSC 2019)
1. Plasticizer
2. Synthetic base stock for industrial lubricating oils and compressor fluids

Known Impurities[4]:
Common impurities may include 1,2-benzenedicarboxylic acid, bis(4-methyl-2-propylhexyl) ester and 1,2-benzenedicarboxylic acid, 4-methyl-2-propylhexyl-2-propylheptyl. Bisphenol A (0.3-0.5%) and Topanol CA (0.1%) may be added as stabilizers, and the remaining fraction of DPHP may contain a maximum of 0.1% water (CPSC 2019).

GreenScreen® Summary Rating for DPHP[5,6 7,8]: DPHP was assigned a **GreenScreen Benchmark™ Score of U** ("Unspecified Due to Insufficient Data") (CPA 2018b)**.** Prior to the data gap analysis, it was assigned a preliminary Benchmark score of 2 ("Use but Search for Safer Substitutes"). This preliminary score is based on the following hazard score:

- Benchmark 2e
    - Moderate Group I Human Toxicity (Developmental toxicity-D, and endocrine activity-D)

[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.

Data gaps (DG) exist for carcinogenicity (C) and neurotoxicity (repeated dose-Nr*). As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis) (CPA 2018b), DPHP does not meet requirements for a GreenScreen® Benchmark Score of 2 due to the hazard data gaps. Therefore, it was assigned a GreenScreen® Benchmark Score of U. In a worst-case scenario, if DPHP were assigned a High score for the data gap C, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for DPHP

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*	*	*								
DG	**L**	**L**	*M*	*M*	**L**	**L**	*M*	*L*	DG	**L**	*L*	**L**	**L**	**L**	**L**	**vL**	**vL**	*L*	**L**

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As DPHP is readily biodegradable meeting the 10-day window, it is not expected to have relevant transformation products.

Introduction

DPHP is an ortho phthalate with a backbone of C7 branched with a propyl side chain. DPHP belongs to the High Molecular Weight Phthalate Esters (HMWPE) group, which are primarily used as industrial chemicals that are associated with polymers to impart flexibility in polyvinyl chloride (PVC) resins. They are also used as synthetic base stocks for industrial lubricating oils and compressor fluids. The United States Food and Drug Administration (U.S. FDA) has also approved DPHP for use in food packaging and handling. Typical concentrations of DPHP in end use products, including automobile undercoating, building materials, wires, cables, shoes, adhesives, pool liners, and gloves, range from 30 to 60%. In general DPHP is manufactured in a closed system by catalytically esterifying phthalic anhydride with isomeric decyl alcohols (CPSC 2019).

ToxServices assessed DPHP 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 2021). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

DPHP 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 2022) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[9] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for DPHP can be found in Appendix C.

- DPHP is a BM-U chemical when screened using Pharos, based on an expired GreenScreen; and therefore, a full GreenScreen® is required.
- DPHP is not listed on the U.S. DOT list.
- DPHP is on the following list for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for DPHP as indicated in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 1: GHS H Statements for DPHP (CAS #53306-54-0) (ECHA 2022a,b)

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

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for DPHP (CAS #53306-54-0)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Wear respiratory protection if ventilation is inadequate; chemical resistant protective gloves; safety glasses with side shields; body protection (based on level of activity and exposure)	BASF 2015	None identified	N/A

Physicochemical Properties of DPHP

DPHP is a clear, colorless, viscous liquid at room temperature. It has negligible solubility in water and its low vapor pressure indicates it is not likely to vaporize. Its measured high partition coefficient (log K_{ow}) of > 6 suggests it may have low bioavailability.

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

Table 3: Physical and Chemical Properties of DPHP (CAS #53306-54-0)		
Property	**Value**	**Reference**
Molecular formula	$C_{28}H_{46}O_4$	ChemIDplus 2022
SMILES Notation	CCCCCC(CCC)COC(=O)c1ccccc1C(=O)OCC(CCC)CCCCC	ChemIDplus 2022
Molecular weight	446.672	ChemIDplus 2022
Physical state	Liquid	ECHA 2022a
Appearance	Clear, colorless, homogenous, viscous liquid	ECHA 2022a
Melting point	-48°C (pour point)	ECHA 2022a
Boiling point	252.5–253.4ºC (decomposes before boiling at atmospheric pressure)	ECHA 2022a
Vapor pressure	0.0000037 Pa at 20°C	ECHA 2022a
Water solubility	< 0 mg/L at 25°C; 0.002 µg/L at 25°C (estimated)	ECHA 2022a
Dissociation constant	N/A	
Density/specific gravity	0.96 g/mL	ECHA 2022a
Partition coefficient	Log K_{ow} > 6 at 25°C and pH = 5.66 (EU Method A.8) Log K_{ow} = 10.36 (estimated)	ECHA 2022a

Toxicokinetics

Absorption

- MAK 2017, CPSC 2019, ECHA 2022a
  - *Oral*: DPHP is absorbed via the oral route as demonstrated in animal studies with repeated oral administration and in humans. Systemic effects were found in animal studies especially in the liver and thyroid gland indicating that oral absorption can be assumed. Similarly, oral absorption was seen in human volunteers (1 male and 5 male) given oral doses of 50 mg deuterium-labeled DPHP (D4-DPHP, deuterium labelling on the aromatic ring) with an average 24% to 34% of the dose eliminated within 48 hours in the urine as specific degradation products. Authors of the REACH registration dossier for DPHP assigned an oral absorption rate of 50% (ECHA 2022a).
  - *Dermal*: *Surrogate: DIDP (CAS #26761-40-0 / 68151-49-1):* Male Fischer 344 rats were administered topical applications of ^{14}C-radiolabeled DIDP (purity not specified) at 5-8 mg/cm^2 under semi-occlusive dressing over seven days. Total DIDP was 82%, with 80% recovered at the application site and 2% recovered in the carcass and excretions. As an index of dermal absorption, 0.5% of the DIDP was absorbed over seven days (Klimisch 2, reliable with restrictions).
  - *Dermal*: *Surrogate: DIDP (CAS #26761-40-0 / 68151-49-1):* ^{14}C-radiolabeled DIDP (purity not specified) was applied to the skin of rats (strain not specified) at 16.3 mg/cm^2. Approximately 93% of the administered dose was recovered at the application site and only trace amounts were recovered in the excreta and other tissues. The total absorbed dose was estimated at 4% of the administered dose (Klimisch 2, reliable with restrictions).
  - *Dermal: Surrogate: DEHP (CAS #117-81-7):* In *vitro* tests with undiluted DEHP show that the dermal absorption rate in the steady state is 4 times higher in rats than for human skin. A similar difference can be expected also for DPHP (Klimisch 2, reliable with restrictions).

- *Inhalation*: There are no toxicokinetic studies available for DPHP following inhalation exposure. However, in the subacute inhalation toxicity study in which male Wistar rats (10/dose) were exposed nose/head only to DPHP at concentrations up to 1,000 mg/m^3 for 5 days, there was an increase in the absolute and relative liver and lung weights at the highest dose, which indicates that the substance can be absorbed by inhalation (Klimisch 2, reliable with restrictions).

Distribution

- No data were identified.

Metabolism

- MAK 2017, CPSC 2019, ECHA 2022a
  - *Oral:* After the ingestion of DPHP by a volunteer, 34% of the dose was recovered in the urine within 61 hours in the form of the secondary metabolites mono(2-propyl-6-hydroxyheptyl) phthalate (OH-MPHP), mono(2-propyl-6-oxoheptyl) phthalate (oxo-MPHP), and mono(2-propyl-6-carboxyhexyl) phthalate (cx-MPHxP). Less than 1% was eliminated with the urine in the form of mono(2-propylheptyl) phthalate (MPHP).
  - *Oral*: In another study investigating the metabolism and excretion of DPHP, six healthy male volunteers were administered DPHP (Palatinol®10-P, purity 98%) or ring-deuterated DPHP orally in an aqueous saccharose solution (70% w/v) at a dose of 0.7 mg/kg. Blood was collected 30 minutes before dosing and at frequent intervals after dosing, through 24 hours. Total urine was also collected frequently, through 46 hours after treatment. The most abundant metabolites in the urine were oxo-MPHP and OH-MPHP (60% and 37% of total urinary amount, respectively), with MPHP and cx-MPHP contributing much smaller amounts. The 22-hour urinary excretion of OH-MPHP correlated well with the areas under the concentration-time curves in blood (AUCs) of MPHP, OH-MPHP, and oxo-MPHP, indicating that OH-MPHP would be a good biomarker for internal dose. The correlation was weaker between levels of oxo-MPHP in urine and blood levels of the three metabolites. The AUCs showed the following order: DPHP > MPHP > oxo-MPHP > OH-MPHP.
  - *Oral*: In a toxicokinetic study, male Wistar (Crl:WI(Han)) rats (3/dose/time point) were administered DPHP as an aqueous emulsion in a 70% saccharose solution via gavage at single doses of 0.7 and 100 mg/kg. Concentration-time courses of DPHP and metabolites were monitored in blood. Metabolites identified in the blood were MPHP, oxo-MPHP, OH-MPHP, and cx-MPHP.$The maximum blood concentrations of the primary metabolite MPHP (-d4) and those of the secondary metabolites OH-MPHP(-d4) and oxo-MPHP(-d4) were reached after about one hour after dosing, independent of the DPHP(-d4) dose. The peaks of cx-MPHP occurred about 2 hours later than those of the other metabolites. Among all compounds, MPHP(-d4) showed the highest maximum levels in blood at both doses. OH-MPHP(-d4)- and cx-MPHP-levels were the second highest. The parent compound DPHP(-d4) showed the lowest maximum levels. Glucuronidation of the monoesters accounted for less than 5% of total compounds. The elimination half-lives of the compounds ranged from 2.3 hours (DPHP) to 8.2 hours (cx-MPHP). The normalized AUCs of the metabolites were lower at the high dose of DPHP than at the low one indicating saturation kinetics of intestinal DPHP hydrolysis. Based on this authors proposed the following metabolic pathway: DPHP is hydrolyzed to MPHP, which can be further metabolized to cx-MPHP or to OH-MPHP. The OH-MPHP can be further oxidized to oxo-MPHP. Both oxo-MPHP and cx-MPHP can be glucuronidated prior to excretion. $
  - Metabolism of DPHP is similar to that of DEHP and involves ester cleavage of the diester to form the mono-ester, followed by oxidation of the remaining alkyl side chain, and potential glucuronidation. However, there are differences in the metabolism of DPHP between rats

and humans such as in the relative amount of DPHP and metabolites in the blood, in the amount of glucuronidation, and in the relative amount of omega-1 and omega oxidation.

Excretion

- CPSC 2019, ECHA 2022a
    - *Oral:* In a human study using 5 male volunteers, the subjects were administered D4-DPHP dissolved in ethanol and mixed in an edible waffle cup at single oral doses of about 50 mg. Urine samples were collected over a period of 48 hours. After 24 hours, 12.6% of the oral dose were excreted as oxo-MPHP, followed by OH-MPHP (9.9%), but only 0.42% as cx-MPHxP. An average 24.7% of the administered dose was recovered in the urine within 48 hours, most of which (22.9%) was eliminated during the first 24 hours. Authors concluded that excretion was rapid with all metabolites detected after 48 hours.
    - *Oral:* In the previously described study in which six healthy male volunteers were administered DPHP (Palatinol®10-P, purity 98%) or ring-deuterated DPHP orally in an aqueous saccharose solution (70% w/v) at a dose of 0.7 mg/kg, only 6.1 ± 3.4 % (range 1.93-10.5%) of the administered dose was excreted in the urine. The authors suggested that the remainder of the dose was excreted in the feces. Of the total excretion observed within 46 hours, 90% had occurred within the first 22 hours.

In summary, absorption of DPHP by the oral and inhalation routes of exposure is expected with an absorption rate of 50% established for the oral route. Absorption for the dermal route is low (4%). Following oral administration in rats and human volunteers, DPHP is extensively metabolized to OH-MPHP and oxo-MPHP with the main excretion pathway of urine. It undergoes ester cleavage of the diester to form the mono-ester, followed by oxidation of the remaining alkyl side chain, and potential glucuronidation. However, there are differences in the metabolism of DPHP between rats and humans such as in the relative amount of DPHP and metabolites in the blood, in the amount of glucuronidation, and in the relative amount of omega-1 and omega oxidation.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): DG
DPHP was assigned a score of for carcinogenicity based on insufficient data for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* MAK – Carcinogen Group 3B – Evidence of carcinogenic effects but not sufficient for classification
    - *Screening:* Not present on any screening lists for this endpoint.
- MAK 2017
    - Authors of MAK classified DPHP as carcinogen Category 3B based on its similar mechanism of action (MOA) with the structurally related surrogate, DEHP (CAS #117-81-7), and the fact that carcinogenicity after long-term exposure is suspected although no study exists. The surrogate DEHP was found to be carcinogenic in the rat liver in long-term studies with the liver tumors are considered to be due to peroxisome proliferation, a MOA not likely to be relevant to human. Accordingly, the authors of MAK classified DEHP as Carcinogen Category 4 (Non-genotoxic carcinogen with low risk under MAK/BAT levels). Both DEHP and DPHP have the same MOA, inducing peroxisome proliferation in the liver. Therefore, DPHP is expected to have similar carcinogenic potential as DEHP. However, it is known from studies in rats with DPHP that it induces peroxisome proliferation in the

liver, at less pronounced effects than that caused by the structurally related DEHP. Thus, as no carcinogenicity study exists for DPHP, the authors of MAK conservatively classified it in Carcinogen Category 3B.

- CPSC 2019
  - There are insufficient data to evaluate the carcinogenic potential of DPHP.
  - *Surrogates: DINP (CAS #28553-12-0) and DEHP (CAS #117-81-7):* In carcinogenicity studies using rats and mice, the oral exposure to DINP and DEHP resulted in increased liver tumors in rats and mice. The liver tumors were primarily related to the induction of peroxisome proliferation, a mode of action not likely to be relevant to humans.
- ECHA 2013
  - *Surrogates: DINP (CAS #28553-12-0) and DIDP (CAS #26761-40-0 / 68151-49-1):* The ECHA review of the carcinogenicity studies of DINP and DIDP indicated that both chemicals have positive carcinogenicity data for multiple sites in animals (liver, kidney and mononuclear cell leukemia (MNCL)). The ECHA authors concluded that the renal tumors observed in male rats are due to an underlying mechanism that is specific to male rats and not relevant to humans (accumulation of α2u-globulin). The liver carcinogenicity was related to peroxisome proliferative effects, which is regarded as not relevant to human health. However, the authors did not exclude the possibility that other pathways that are relevant to humans could exist such as PPARα-independent. With regard to MNCL, more recent data indicated that there may be a human counterpart to MNCL in humans. Based on that the ECHA authors concluded that the carcinogenicity of DINP and DIDP remain inconclusive.
- Based on the weight of evidence, a Data Gap was assigned. There are no data available for DPHP, but DPHP is classified as a MAK Group 3B Carcinogen, which corresponds to a GreenScreen® score of Moderate. The MAK (2017) assessment relied on the carcinogenicity data for the surrogate DEHP (CAS #117-81-7); which is listed under Proposition 65 as a carcinogen (Pharos 2022). This corresponds to a GreenScreen® score of High for DEHP. The authors of the U.S. CPSC concluded that there are insufficient data to evaluate the carcinogenicity of DPHP as its surrogates, DINP and DEHP, have caused liver tumors in rats and mice through a MOA (peroxisome proliferation) that is not relevant to humans. The surrogate DINP is also listed under Proposition 65 as a carcinogen. However, the European Chemical Agency (ECHA), another authoritative body, reviewed the carcinogenicity studies for the surrogates, DEHP, DINP, and the isomer DIDP (ECHA 2013, 2016a) and concluded that their carcinogenicity potential remains inconclusive due to the fact that pathways other than peroxisome proliferation which is relevant to humans may exist for the liver tumors observed in rasH2 rats. Therefore, although the MAK 3B classification corresponds to a Moderate, there are no experimental data available for the target, and the authoritative classifications for some surrogate phthalates correspond to a High. However, there are inconsistent conclusions among various authoritative bodies regarding the carcinogenic potential of the surrogates. Due to the considerable uncertainty that remains regarding the carcinogenic potential of DEHP and DINP, in addition to the inherent uncertainty in use of a surrogate, ToxServices did not consider classifications for the surrogates sufficient to warrant a High score for DPHP. Based on the lack of experimental data on DPHP, the CPSC conclusion that there are insufficient data to evaluate the carcinogenicity of DPHP, and ECHA's conclusion that carcinogenicity data on surrogate phthalates are inconclusive, ToxServices concluded that available data are insufficient to assign a reliable classification for DPHP and assigned a Data Gap.

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

DPHP was assigned a score of Low for mutagenicity/genotoxicity based on negative results in *in vitro* mutagenicity and clastogenicity assays with the target and *in vivo* assays with surrogates. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and negative for both chromosomal aberrations and gene mutations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on high-quality data for the target compound and support from surrogates.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a
  - *In vitro:* DPHP was negative for mutagenicity in a GLP-compliant OECD Guideline 471 Ames bacterial reverse mutation assay in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 at concentrations of 10, 100, 500, 2,500, and 5,000 µg/plate with and without metabolic activation (Aroclor 1254-induced rat liver S9-mix). No cytotoxicity was observed; however, precipitate was found at ≥500 µg/plate. There were no increases in the frequency of revertants observed in any strain at any concentration with or without metabolic activation. The positive and vehicle controls were valid (Klimisch 2, reliable with restrictions).
  - *In vitro:* DPHP (purity not reported) was negative for mutagenicity in a GLP-compliant bacterial mutagenicity assay conducted according to OECD Guideline 471 in which *E. coli* strain WP2 uvrA was exposed to the test substance at concentrations of 33, 100, 333, 1,000, 2,500, and 5,000 µg/plate with and without metabolic activation. There were no increases in the frequency of revertants observed in any strain at any concentration with or without metabolic activation. The positive, vehicle, and untreated negative controls were valid (Klimisch 1, reliable without restriction).
  - *In vitro:* DPHP was negative for clastogenicity in a GLP-compliant OECD Guideline 473 chromosome aberration assay in Chinese hamster lung fibroblast (V79) cells at concentrations of 75, 150, 300, 2,600, 3,900, and 5,200 µg/mL with and without metabolic activation (S9 mix). No cytotoxicity was observed; however, precipitation occurred at ≥150 µg/mL. There were no increases in the frequency of aberrations at any concentration with or without metabolic activation. The positive and vehicle controls were valid (Klimisch 1, reliable without restriction).
  - *In vitro:* DPHP was negative for mutagenicity in a GLP-compliant OECD Guideline 476 mammalian cell gene mutation assay in Chinese hamster ovary (CHO) cells. Two separate experiments were performed. In experiment 1, cells were exposed to DPHP at concentrations of 0, 325, 650, 1,300, 2,600, 3,900, and 5,200 µg/mL with and without metabolic activation (liver S9 mix) for 4 hours. In experiment 2, cells were exposed to DPHP at concentrations of 0, 162.5, 325, 650, 2,600, 3,900, and 5,200 µg/mL without metabolic activation for 24 hours, and concentrations of 0, 162.5, 325, 650, and 5,200 µg/mL with metabolic activation (S9) for 4 hours. No cytotoxicity was observed; however, precipitation occurred at ≥150 µg/mL. There were no increases in the frequency of mutants observed at any concentration with or without metabolic activation in either experiment. The positive and vehicle controls were valid (Klimisch 1, reliable without restriction).
  - *In vivo*: *Surrogate: DIDP (CAS #26761-40-0 / 68515-49-1):* Negative results for clastogenicity were reported in a GLP-compliant micronucleus test conducted according to OECD Guideline 474. Male and female CD-1 mice (5/sex/dose group) were administered single oral gavage doses of diisodecylphthalate (purity not specified) in Duke's corn oil at

1,250, 2,500, or 5,000 mg/kg. The animals were sacrificed 24, 48, or 72 hours following dosing and femoral bone marrow samples were isolated for the assessment of micronuclei. No increase in the frequency of micronuclei was observed with treatment. Vehicle and positive control were valid (Klimisch score 2, reliable with restrictions).

- *In vivo*: *Surrogate: DINP (CAS #28553-12-0)*: Negative results for clastogenicity were reported in a micronucleus test (GLP status and guideline not specified). Male CD-1 mice (5/sex/dose group) were administered two oral gavage doses of diisononylphthalate (purity and vehicle not specified) at 500, 1,000, or 2,000 mg/kg on consecutive days. The animals were sacrificed one day following dosing and femoral bone marrow samples were isolated for the assessment of micronuclei. No increase in the frequency of micronuclei was observed with treatment. A positive control was included but results are not specifically stated (Klimisch score 2, reliable with restrictions).

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

DPHP was assigned a score of Low for reproductive toxicity based on the lack of effects to fertility and reproductive function and performance in a two-generation study in rats. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on a high quality study on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a, CPSC 2019
  - A GLP-compliant OECD Guideline 416 two-generation reproductive toxicity study was conducted with male and female Wistar rats (25/sex/dose). Animals were administered DPHP in the feed at doses of 0, 40, 200 and 600 mg/kg/day over the two parental generations (F0 and F1). F0 animals were exposed for a total of 126 days and F1 animals were exposed for a total of 131 days. Animals were observed for mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, estrous cyclicity, sperm parameters, and reproductive indices. Litters were observed for number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, weight gain, physical or behavioral abnormalities, organ weight, external and internal abnormalities, and viability indices. After sacrifice, gross and histopathological examinations were performed on parents and offspring. There were no effects on fertility or reproductive function and performance in any dose group of the F0 and F1 generations. The authors reported a reproductive NOAEL of 600 mg/kg/day, the highest dose tested, for this study (Klimisch score 1, reliable without restriction).

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

DPHP was assigned a score of Moderate for developmental toxicity based on decreased pup body weight and body weight gain in a two-generation study in rats, and minimal skeletal malformations observed in a prenatal developmental toxicity study in rats, both occurring in the presence of parental systemic toxicity. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when limited or marginal evidence of developmental toxicity in animals (CPA 2018b). The confidence in the score is low as it is unclear if the observed effects are secondary to parental systemic toxicity rather than specific developmental toxicities and due to lack of neurobehavioral examination in the available developmental toxicity studies, since the observations of thyroid effects in repeated dose

toxicity studies suggest the potential for neurodevelopmental effects secondary to thyroid hormone disruption.

- 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 2022a, CPSC 2019
    - In the previously described GLP-compliant OECD Guideline 416 two-generation reproductive toxicity study with male and female Wistar rats (25/sex/dose), animals were administered DPHP in the feed at doses of 0, 40, 200 and 600 mg/kg/day over the two parental generations (F0 and F1). F0 animals were exposed for a total of 126 days, F1 animals were exposed for a total of 131 days. Animals were observed for mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, estrous cyclicity, sperm parameters, and reproductive indices. Litters were observed for number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, weight gain, physical or behavioral abnormalities, organ weight, external and internal abnormalities, and viability indices. After sacrifice, gross and histopathological examinations were performed on parents and offspring. At a dose of 600 mg/kg/day, the F1 and F2 generation pups had a statistically significant decrease in body weight and body weight gain. No other adverse effects to reproduction or development were reported. The authors established a parental systemic toxicity NOAEL of 40 mg/kg/day based on evidence of peroxisome proliferation in the liver, bones, kidneys and thyroid, and reduced body weight without changes in food consumption. Based on the decrease in pup body weight and body weight gain, the authors established a developmental NOAEL of 200 mg/kg/day for this study (Klimisch score 1, reliable without restriction).
    - A GLP-compliant OECD Guideline 414 prenatal developmental toxicity study was conducted with pregnant female Wistar rats (25/dose). Animals were administered DPHP at doses of 0, 40, 200 and 1,000 mg/kg/day via oral gavage on gestation days (GDs) 6-19, and sacrificed on GD 20. Animals were observed for mortality, clinical signs, body weight, food consumption, and ovary and uterine content. Fetuses were examined for external, soft tissue, skeletal, and head abnormalities. Food consumption and body weight were reduced at the high dose. Also at the high dose, significant changes were observed on gravid uterus weight, resorptions, and post implantation loss value. Fetal examinations revealed a borderline effect of skeletal malformations. Study authors reported a developmental NOAEL and LOAEL of 200 and 1,000 mg/kg based on the reported effects. The study authors identified a NOAEL of 200 mg/kg/day for maternal toxicity based on transient reduction in food consumption and reduced body weight (Klimisch score 1, reliable without restriction).
    - A second GLP-compliant OECD Guideline 414 prenatal developmental toxicity study in pregnant female Wistar rats (10/dose) was reported in the REACH dossier that following the same guidelines and dose levels as described above; however, exposure was on GDs 6-15. No effects were observed on developmental toxicity and a NOAEL of 1,000 mg/kg was reported (Klimisch score 2, reliable with restrictions).
    - A GLP-compliant OECD Guideline 414 prenatal developmental toxicity study was conducted with pregnant female New Zealand White rabbits (25/dose). Animals were administered DPHP at doses of 0, 33.4, 65.7, and 126.8 mg/kg/day in the diet on GDs 6-29, and sacrificed on GD 29. Animals were observed for mortality, clinical signs, body weight, food consumption, and ovary and uterine content. Fetuses were examined for external, soft tissue, skeletal, and head abnormalities. Treatment caused maternal toxicity at the high-dose

group as characterized by reduced food consumption and mean and average body weight gain. There were no treatment related effects on fetal morphology and a NOAEL for developmental toxicity of 127mg/kg/day, which was the highest dose tested, was reported. The study authors identified a NOAEL of 66 mg/kg/day for maternal toxicity based on transient reduction in food consumption and reduced body weight (Klimisch score 1, reliable without restriction).

- Based on the weight of evidence, a score of Moderate was assigned. Although no developmental effects were observed in a prenatal developmental toxicity study in rabbits, the doses applied were relatively low (127 mg/kg/day). Developmental effects, such as decreased offspring body weight and marginal increase in skeletal variations, were reported in the 2-generation toxicity study and the prenatal developmental toxicity studies in rats. While these effects occurred at maternally toxic doses and are potentially secondary to maternal toxicity, in the absence of conclusive data demonstrating they are not direct developmental effects, a score of Moderate is warranted based on limited or marginal evidence of developmental toxicity. In addition, the observations of thyroid effects in the repeated dose toxicity studies (see below) suggests the potential for neurodevelopmental effects secondary to thyroid hormone disruption (CPSC 2019). The MOA for the observed thyroid effects is unknown and none of the available developmental toxicity studies included neurobehavioral examinations. Therefore, the possibility of DPHP to cause adverse neurodevelopmental effects is uncertain. Accordingly, ToxServices assigned a score of Moderate for this endpoint based on the limited or marginal evidence of developmental toxicity seen in the studies performed with rats, and reduced the confidence because it is unclear if effects are secondary to maternal toxicity and there are no data available regarding developmental neurotoxicity.

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

DPHP was assigned a score of Moderate for endocrine activity based on effects in the pituitary and the thyroid gland seen in *in vivo* studies suggesting that it may have endocrine disrupting properties. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when there is evidence of endocrine activity (CPA 2018b). Because these effects are not associated with any adverse effects corresponding to a High classification for other endpoints, the score of Moderate is not modified to a High. The confidence in the score is reduced as the MOA for the observed effects is unknown, making it difficult to consider the human relevance and implications of the observed changes.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CPSC 2019, ECHA 2022a
  - *Oral*: In the previously described GLP-compliant OECD Guideline 416 two-generation reproductive toxicity study with male and female Wistar rats (25/sex/dose), animals were administered DPHP in the feed at doses of 0, 40, 200, and 600 mg/kg/day over the two parental generations (F0 and F1). F0 animals were exposed for a total of 126 days, F1 animals were exposed for a total of 131 days. Treatment caused a significant increase in the thyroid weight (unclear whether this was absolute or relative) of high-dose F0 females. In the F1 generation, absolute and relative thyroid weight was significantly increased in females at the high dose and in males at all doses, but the changes was not dose-related. There were no changes reported on thyroid histopathology in the F0 generation, but thyroid follicular hypertrophy/hyperplasia was observed in both males and females at the mid- and high-doses. The LOAEL for males was 40 mg/kg/day based on increased thyroid weight; there was no NOAEL. The NOAEL and LOAEL for females were 40 mg/kg/day and 200 mg/kg/day, respectively, based on thyroid follicular hypertrophy/hyperplasia.

  - *Oral:* In a GLP-compliant 90-day repeated dose toxicity study conducted according to OECD Guideline 408, male and female Wistar rats (10/sex/group) were administered DPHP (98.7% purity) in the feed at doses of 500, 2,500 and 15,000 ppm (reported as equivalent to 36, 181, and 1,187 mg/kg/day, respectively, in males, and 42, 211, and 1,344 mg/kg/day, respectively, in females) for 3 months. The study did not include measurements of thyroid weight and thyroid hormone levels. However, treatment caused thyroid hypertrophy in mid- and high-dose males and females, which CPSC reported is consistent with increased thyroid hormone clearance secondary to liver enzyme induction, followed by compensatory changes in the thyroid. Increase in basophilic cells in the anterior part of the pituitary gland, which produce thyroid stimulating hormone that activates the thyroid to release more T3 and T4, of males at mid and high dose groups were also reported (3/10 at the mid dose, 8/10 at the high dose). Treatment also caused a statistically significant decrease in absolute adrenal weight (15.5%) in males at the high dose. CPSC determined that the NOAEL for findings in thyroid gland and pituitary was the lowest dose tested (36 mg/kg/day in males, 42 mg/kg/day in females). CPSC also stated that the effects on the thyroid and pituitary are potentially secondary to increased thyroid hormone clearance and thus potentially not relevant to humans, but because the MOA had not been demonstrated for DPHP, these effects are assumed to be relevant.
  - Based on the above data, authors of the U.S. CPSC concluded that thyroid is a target organ for effects of DPHP, noting that the pituitary gland changes (increased basophilic cells) seen in the subchronic Wistar rat study and the thyroid follicular hypertrophy/hyperplasia seen in that study and the two-generation study may have been secondary to induction of liver metabolic enzymes (e.g., UGT) by PPARα or CAR. According to this MOA, thyroid hyperplasia and tumors in rodents are the result of increased hepatic clearance of T3 and T4 leading to a compensatory increase in TSH followed by thyroid hypertrophy. As indicated by CPSC, this MOA is not relevant to humans for tumorigenesis, but it is relevant for neurodevelopmental effects. As no measurement of the thyroid hormone levels were conducted in the available animal studies and due to the lack of inhibitor studies, it is difficult to consider the human relevance and implications of the observed changes. Therefore, the *in vivo* data suggest that DPHP does have an endocrine active effect.
- ECHA 2014, 2016b
  - DPHP is a potential endocrine disruptor and is under ECHA's evaluation for endocrine disruption as the observed effects in the pituitary and the thyroid gland raise a concern that sensitive life stages of different animal species may be affected.

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): L

DPHP was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values of > 5,000 mg/kg in rats and >2,000 mg/kg in rabbits, respectively, and an inhalation LC_{50} of >5 mg/L/4h in rats. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg and inhalation (dust/mist/fume) LC_{50} values are greater than 5 mg/L (CPA 2018b). The confidence in the score is high as it is based on high quality data for the target compound.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a, CPSC 2019
  - *Oral:* LD_{50} (male and female Sherman Wistar rat) >5,000 mg/kg
  - *Dermal:* LD_{50} (male and female Albino rabbit) > 2,000 mg/kg
  - *Inhalation (aerosol, dust):* LC_{50} (male and female albino rat) > 20.5 mg/L/1hr (calculated to >5 mg/L/4h according to GHS).

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

DPHP was assigned a score of Low for systemic toxicity (single dose) based on the lack of systemic effects in acute oral and dermal toxicity studies at doses greater than the guidance value of 2,000 mg/kg and in an acute inhalation study at concentrations of >5 mg/L/4h (mist). GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on experimental data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a, CPSC 2019
  - *Oral:* In an acute oral toxicity study conducted similar to OECD Guideline 401, male and female Sherman Wistar rats (5/sex/dose) were administered a single dose of 5,000 mg/kg DPHP via oral gavage and observed for 14 days. There were no mortalities and no unusual behavioral signs reported. There were no effects to body weight and gross pathological examination revealed nothing remarkable. The authors identified an LD_{50} of >5,000 mg/kg (Klimisch 2, reliable with restrictions).
  - *Dermal:* In an acute dermal toxicity study conducted similar to OECD Guideline 402, male and female Albino rabbits (3/sex/dose) were administered 2,000 mg/kg DPHP for 24 hours under occlusive conditions and were observed for 14 days. There were no mortalities and no unusual behavioral signs reported. There were no effects to body weight and gross pathological examination revealed nothing remarkable. The authors identified an LD_{50} of >2,000 mg/kg (Klimisch 2, reliable with restrictions).
  - *Inhalation (aerosol, dust):* In an acute inhalation toxicity study conducted similar to OECD Guideline 403, male and female albino rats (5/sex/dose) were exposed whole body to DPHP aerosol at a concentration of 20.5 mg/L for 1 hour, and were observed for 14 days. There were no mortalities. Clinical signs immediately after exposure included wet, ruffled fur, agitation, and raspy sounds, that cleared by 24 hours. There were no effects to body weight and gross pathological examination revealed nothing remarkable. The authors identified a 1 hour LC_{50} of >20.5 mg/L, and calculated a 4 hour LC_{50} of > 5 mg/L according to GHS (Klimisch 2, reliable with restrictions).

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

DPHP was assigned a score of Moderate for systemic toxicity (repeated dose) based on ToxServices conservatively classifying it to GHS Category 2 with oral NOAEL values of 39 and 40 mg/kg/day and LOAEL values of 196 and 420 mg/kg/day identified in two 90 day oral studies in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when systemic toxicity is observed between the Guidance values of 10 and 100 mg/kg/day for oral 90 day studies and

when they are classified to GHS Category 2 (CPA 2018b). The confidence in the score is low because it is not possible to conclusively determine if effects would have occurred below the Guidance value.

- 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 2022a, CPSC 2019
    - *Oral:* In a GLP-compliant 90-day repeated dose toxicity study conducted according to OECD Guideline 408, male and female Wistar rats (10/sex/group) were administered DPHP (98.7% purity) in the feed at doses of 500, 2,500 and 15,000 ppm (reported as equivalent to 36, 181, and 1,187 mg/kg/day, respectively, in males, and 42,211, and 1,344 mg/kg/day, respectively, in females) for 3 months. Animals were observed for mortality, clinical signs, body weight, food consumption and efficiency, hematology, clinical chemistry, and urinalysis. Additionally, ophthalmoscopic, gross pathology, and histopathology examinations were performed. At all doses no deaths occurred and no significant clinical signs or effects to food consumption or efficiency were reported. A slight decrease in body weight gain was reported in the high dose animals. In the high dose group, clinical findings including hematology and urinalysis showed significantly decreased hemoglobin concentrations, decreased hematocrit values (males only), increased platelet counts (males only), decreased mean corpuscular hemoglobin (females only), decreased chloride concentrations (females only), increased albumin levels (males only), decreased triglycerides (males only), increased creatinine (females only), decreased glucose levels (females only), increased alkaline phosphatase, increased cyanide-insensitive palmitoyl-CoA-oxidation, and increased urinary volumes. In the mid dose group, increases in magnesium and liver cyanide-insensitive palmitoyl-CoA-oxidation were reported in females and increased albumin was reported in males. High dose animals also had significantly increased absolute and relative liver weights, decreased absolute adrenal weight (males only), and increased relative kidney and brain weights. Mid dose animals had increased absolute liver weight in females and relative liver weight in males. No effects were reported in ophthalmoscopic or gross pathology examinations. Histopathology revealed liver cell hypertrophy due to peroxisome proliferation, an increase in basophilic thyreotrophic cells in the pituitary gland (males only), and hypertrophy of the follicular epithelium of the thyroid gland in both high and mid dose animals. Based on liver changes, a NOAEL and LOAEL of 39 and 196 mg/kg were reported; however, the study authors reported that the liver effects may have been the result of peroxisome proliferation and the relevance of these effects to humans is not known. Based on this, the authors reported a NOAEL and LOAEL for hazards relevant to human of 196 and 1,266 mg/kg/day, respectively, based on the hematological effects, disregarding the peroxisome proliferation (Klimisch 1, reliable without restriction).
        - *As the NOAEL and LOAEL of 39 and 196 mg/kg/day straddle the GHS Guidance value of 100 mg/kg/day for Category 2, data are insufficient to determine if adverse effects would occur at doses below 100 mg/kg/day. ToxServices conservatively classified DPHP as a GHS Category 2 based on the results of this study.*
    - *Oral:* A second subchronic repeated dose toxicity study was conducted using male and female Alpk:ApfSD rats (12/sex/group). Rats were administered DPHP in the diet at doses of 0, 500, 5,000, and 12,000 ppm (reported as equivalent to 0, 40, 420, and 1,000 mg/kg/day) for 14 weeks. Animals of the control and high dose groups were subject to a 4-week post exposure recovery period. Animals were observed for mortality, body weight, feed consumption, hematology, and clinical chemistry. Additionally, gross pathology, and histopathology examinations were performed. A significant decrease in body weight gain

and feed consumption was noted in the high dose animals; however, this effect was partially resolved by then end of the recovery period. Mid dose males had a slight, but not significant reduction in body weight gain. Hematology revealed reduced red blood cell count, hemoglobin, and hematocrit in high dose animals and mid dose males. Clinical chemistry showed a decrease in plasma sodium, cholesterol and triglycerides and an increase in plasma potassium concentrations and cyanide insensitive palmitoyl CoA activity in high dose animals, and increased cyanide insensitive palmitoyl CoA activity and decreased plasma cholesterol and triglycerides in mid dose animals. Histology revealed lesions in the zona glomerulosa of the adrenal glands (minimal in mid dose, and moderate at high dose). Increases in liver weights and increases in peroxisome enzyme levels were reported in all treatment groups. However, peroxisome proliferation was only noted in the mid and high-dose groups. Based on available data, a NOAEL and LOAEL of 40 and 420 mg/kg were reported by study authors for effects on hematological parameters and liver (Klimisch 2, reliable with restrictions).

- *Although the LOAEL of 420mg/kg/day is above the GHS Guidance value of 100 mg/kg/day for Category 2, the NOAEL of 40 mg/kg/day is below the cut-off value. Therefore data are insufficient to determine if adverse effects would occur at doses below 100 mg/kg/day. ToxServices conservatively classified DPHP as a GHS Category 2 based on the results of this study.*

- *Inhalation (aerosol):* In a GLP-compliant subacute toxicity study, male Wistar rats (10/dose) were exposed nose/head only to DPHP at concentrations of 50, 250, and 1,000 mg/m^3 6 hours/day for 5 consecutive days. Animals were observed for mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, acute phase proteins and palmitoyl CoA oxidation. Additionally, gross pathology and histopathology examinations were performed. There were no mortalities or clinical signs reported and no treatment-related changes to hematology. The mean body weight change was slightly, but significantly lower in the high dose group. Effects to acute phase protein levels were observed; however, there was no pathophysiological correlate. Clinical chemistry showed decreased globulin and total protein levels and increased cholesterol levels in the high dose group. Pathological examination revealed increased relative and absolute lung and liver weights and signs of respiratory irritation in both the high and mid dose groups. The high dose group also had slight diffuse hepatocellular hypertrophy in male animal's livers. Based on the above effects, the authors reported a systemic toxicity NOAEC and LOAEC of 250 and 1,000 mg/m^3 (equal to 0.25 and 1 mg/L, respectively) for this study.
    - *Due to the shorter duration of this study, the guidance values were multiplied by 18 (i.e., 0.2 mg/L/6h/day (mist)* 18 = 3.6 mg/L/6h/day) as 90 days is approximately 18 times the duration of 5 days. As the LOAEC of 1 mg/L is within the GHS adjusted Guidance values of 0.36-3.6 mg/L/6h/day for Category 2, ToxServices classified DPHP as a GHS Category 2 based on the results of this study. The NOAEC of 0.25 mg/L is however below the cut-off value of 0.36 mg/L/6h/day. Therefore, there is insufficient information to concluded that adverse effects do not occur at 0.36 mg/L.*

- Based on the weight of evidence, a score of Moderate was assigned. The oral LOAELs of 196 and 420 mg/kg/day identified in the two subchronic toxicity studies with rats are greater than the oral GHS Guidance value of 100 mg/kg/day in a 90-day study, but because the NOAELs (39 and 40 mg/kg/day, respectively) are within the GHS Guidance values for Category 2 it is not possible to conclusively determine if effects would have occurred between 10 mg/kg/day and 100 mg/kg/day. ToxServices conservatively classified DPHP as a GHS Category 2 based on the oral studies to be protective of human health. Additionally, the inhalation LOAEC of 1 mg/L identified in the

subacute study in rats is within the GHS adjusted Guidance values for Category 2 of 0.36 – 3.6 mg/L, but because the NOAEC (0.25 mg/L) is below the guidance value range for Category 2 it is not possible to conclusively determine if effects would have occurred below 0.36 mg/L. However, due to the very short duration of the inhalation study, ToxServices placed more weight in the oral 90 day studies. Therefore, a score of Moderate was assigned.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
DPHP was assigned a score of Low for neurotoxicity (single dose) based on the lack of neurotoxic effects in acute oral, dermal, and inhalation toxicity studies at doses greater than the GHS Guidance values. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate negative data are available and they are not GHS-classified (oral and dermal NOAEL > 2,000 mg/kg and inhalation NOAEC > 5 mg/L/4h for mist) (CPA 2018b). The confidence in the score is low because it is based on studies with limited neurotoxicity examination.

- 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 2022a, CPSC 2019
  - *Oral:* In the previously described acute oral toxicity study conducted similar to OECD Guideline 401, male and female Sherman Wistar rats (5/sex/dose) were administered a single dose of 5,000 mg/kg DPHP via oral gavage and observed for 14 days. There were no mortalities or clinical signs of neurotoxicity. There were no effects to body weight and gross pathological examination revealed nothing remarkable. The authors identified an LD_{50} of > 5,000 mg/kg (Klimisch 2, reliable with restrictions). *Clinical signs of neurotoxicity often evaluated in animal studies include: drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness, lethargy, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure. As animals in this study did not show any of these signs, ToxServices concluded that the test substance was not neurotoxic in this study.*
  - *Dermal:* In the previously described acute dermal toxicity study conducted similar to OECD Guideline 402, male and female Albino rabbits (3/sex/dose) were administered 2,000 mg/kg DPHP for 24 hours under occlusive conditions and were observed for 14 days. There were no mortalities and no unusual behavioral signs reported. There were no effects to body weight and gross pathological examination revealed nothing remarkable. The authors identified an LD_{50} of >2,000 mg/kg (Klimisch 2, reliable with restrictions).
  - *Inhalation (aerosol, dust):* In the previously described acute inhalation toxicity study conducted similar to OECD Guideline 403, male and female albino rats (5/sex/dose) were exposed whole body to DPHP aerosol at a concentration of 20.5 mg/L for 1 hour, and were observed for 14 days. There were no mortalities or clinical signs of neurotoxicity. There were no effects to body weight and gross pathological examination revealed nothing remarkable. The authors identified a 1 hour LC_{50} of >20.5 mg/L, and calculated a 4 hour LC_{50} of > 5 mg/L according to GHS (Klimisch 2, reliable with restrictions).

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

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.

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

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
DPHP was assigned a score of Low for skin sensitization based on negative results in a modified Buehler test in guinea pigs. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on a well conducted study for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a, CPSC 2019
  - DPHP (91.3% purity) was non-sensitizing to guinea pigs in a modified Buehler test similar to OECD Guideline 406. Animals (5/sex) were epicutaneously induced with undiluted DPHP under occlusive conditions 10 times for 24 hours each; following a two-week rest period, animals were epicutaneously challenged with undiluted DPHP under occlusive conditions for 24 hours. There were no positive reactions reported (Klimisch 2, reliable with restrictions).

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
DPHP was assigned a score of Low for respiratory sensitization based on a lack of structural alerts and reports of respiratory sensitization and negative results for skin sensitization, according to ECHA's guidance. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- 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
  - DPHP does not contain any structural alerts for respiratory sensitization (Appendix D)
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA 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). As DPHP was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by DPHP, and as DPHP does not contain any structural alerts for respiratory sensitization (OECD 2021), DPHP is not expected to be a respiratory sensitizer. Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L
DPHP was assigned a score of Low for skin irritation/corrosivity based on negative results in acute dermal irritation studies with rabbits. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative and they are not GHS classified

(CPA 2018b). The confidence in the score is high as it is based on high quality data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a, CPSC 2019
  - DPHP was not irritating in a GLP-compliant OECD Guideline 404 acute dermal irritation study. Male and female New Zealand rabbits (1 male, 2 female) were administered 0.5 mL unchanged DPHP to clipped skin of the rear flank under semi-occlusive conditions for 4 hours. The skin sites were evaluated 1, 24, 48, and 72 hours following patch removal. Slight erythema was observed in all animals; however the effect was reversible within 48 hours. The mean erythema and edema scores were 0.1 and 0, respectively. DPHP was reported to be non-irritating by the study authors (Klimisch 1, reliable without restriction).
  - In a second study, unchanged DPHP (91.3% purity) was applied to intact and abraded skin on the backs of 6 albino rabbits for 24 hours under occlusive conditions. No signs of irritation were observed; the mean erythema and edema scores and the primary dermal irritation index were all 0. Study authors reported DPHP as negative for irritation (Klimisch 2, reliable with restrictions).

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

DPHP was assigned a score of Low for eye irritation/corrosivity based on negative results in ocular irritation studies with rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on high quality data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a, CPSC 2019
  - DPHP was not irritating in a GLP-compliant OECD Guideline 405 acute eye irritation/corrosion study. One eye of male and female New Zealand rabbits (1 male, 2 female) was instilled with 0.1 mL unchanged DPHP for a 24-hour period. Rabbits were then observed for 72hr. Slight to moderate conjunctival redness and slight discharge were observed within the initial 24 hour period. All effects were reversible within 48 hours. The mean cornea opacity, iris, conjunctivae and chemosis scores were 0/4, 0/2, 0.3/3, and 0/4, respectively. The study authors concluded that DPHP was not irritating to the eyes of rabbits (Klimisch 1, reliable without restriction).
  - In a second study, one eye of male and female albino rabbits (3/sex) was instilled with 0.1 g unchanged DPHP (91.3% purity) and rabbits were observed for 7 days. No tissues observed showed any effects after 1, 24, 48, or 72 hours. The mean cornea opacity, iris, conjunctivae and chemosis scores were all 0. The study authors concluded that DPHP was not irritating to the eyes of rabbits (Klimisch 2, reliable with restrictions).

Ecotoxicity (Ecotox)

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

DPHP was assigned a score of Low for acute aquatic toxicity based on L/EC_{50} values that exceed 100 mg/L or the limit of solubility in fish, daphnia, and algae for the target chemical and its surrogate.

GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are >100 mg/L for all three trophic levels (CPA 2018). The confidence in the score is high as it is based on high quality data for the target chemical and 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 2022a (Note: Only studies reported in the REACH dossier with a reliability rating of 1 (reliable without restrictions) or 2 (reliable with restrictions) were included in the assessment)
  - 48-hour EC_{50} (*Daphnia magna,* daphnia) > 100 mg/L (GLP, EU Method C.2) (Klimisch 1, reliable without restriction).
  - 72-hour EC_{50} (*Scenedesmus subspicatus*, green algae) > 100 mg/L (growth rate and biomass) (GLP, EU Method C.3) (Klimisch 1, reliable without restriction).
- ECHA 2022c
  - *Surrogate: DINP (CAS #28553-12-0):*
    - DINP has a measured water solubility of 0.6 µg/L (0.0006 mg/L) at 21°C as identified in a non-GLP-compliant test conducted in a manner similar to OECD Guideline 105.
    - 96-hour LC_{50} (*Danio rerio*, zebrafish) > 102 mg/L (measured, combined with an emulsifier) (GLP-compliant, EU Method C.1)
    - 96-hour LC_{50} (*Lepomis macrochirus*, bluegill) > 0.14 mg/L (measured, highest achievable concentration) (GLP-compliant, U.S. EPA 660/3-75-009)
    - 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) > 0.19 mg/L (measured, highest achievable concentration) (GLP-compliant, U.S. EPA 660/3-75-009)
    - 96-hour LC_{50} (*P. promelas*, fathead minnow) > 0.1 mg/L (measured, highest achievable concentration) (GLP-compliant, U.S. EPA 660/3-75-009)
    - 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) > 0.16 mg/L (measured, highest achievable concentration) (GLP-compliant, U.S. EPA 660/3-75-009)
    - 96-hour LC_{50} (*Cyprinodon variegatus*, sheepshead minnow) > 0.52 mg/L (measured, highest achievable concentration (GLP-compliant, 660/3-75-009)

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

DPHP was assigned a score of Low for chronic aquatic toxicity based on NOEC values that exceed 10 mg/L or the limit of solubility in fish, daphnia, and algae. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L, or no effects are observed at saturation (CPA 2018). The confidence in the score is high as it is based on high quality data for all three trophic levels.

- 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 2022a
  - 36-day NOEC (*Danio rerio*, fish) > 10 mg/L. No adverse effects observed on the time to hatch, hatching success, survival or growth (GLP, OECD Guideline 210) (Klimisch 1, reliable without restriction).
  - 21-day NOEC (*D. magna,* daphnia) > 1 mg/L for reproduction (non-GLP, OECD Guideline 211) (Klimisch 2, reliable with restrictions).
    - The water solubility for DPHP is 0.002 µg/L at 25°C.
  - 72-hour NOEC (*S. subspicatus*, green algae) = 25 mg/L (GLP, EU Method C.3) (Klimisch 1, reliable without restriction).

Environmental Fate (Fate)

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

DPHP was assigned a score of Very Low for persistence based on being readily biodegradable meeting the 10-day window in an OECD Guideline 301B CO_2 Evolution Test, and predictions that it will mainly partition to sediment. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when they are readily biodegradable and meet the 10-day window, and they mainly partition to soil, water or sediment (CPA 2018b). The confidence in the score is high as it is based on a high quality study for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a
  - DPHP was readily biodegradable and met the 10-day window in a GLP-compliant OECD Guideline 301B CO2 Evolution Test. In this study, aerobic, domestic, non-adapted, activated sludge was exposed to 13 mg/L of the test substance for 28 days. The test substance degraded 80-90% in 28 days and met the 10-day window (Klimisch 1, reliable without restriction).
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that DPHP is expected to be readily biodegradable. Fugacity modeling (EQC default method) predicts 65% will partition to sediment with a half-life of 3,240 hours (135 days), 31.2% will partition to soil with a half-life of 720 hours (30 days), and 3.57% to water with a half-life of 360 hours (15 days) (Appendix E).

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

DPHP was assigned a score of Very Low for bioaccumulation based on an estimated BAF of 13.27 and a measured BCF) < 3 in rainbow trout for a surrogate. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the BAF value is less than or equal to 100 (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 list s for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a
  - DPHP has a log K_{ow} of > 6 at 25°C as identified in a HPLC method conducted according to GLP and EU Method A.8 test (Klimisch 1, reliable without restriction).
- U.S. EPA 2017
  - BCFBAF predicts a BAF of 13.27 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration and based on a modeled log K_{ow} of 10.48 (Appendix E).
- ECHA 2022c
  - <u>*Surrogate: DINP (CAS #28553-12-0):*</u> A non-GLP-compliant bioaccumulation study was performed with rainbow trout (*Oncorhynchus mykiss*) exposed to DINP (purity not specified) in feed at a nominal concentration of 1,200 ppm for 14 days. A depuration period of 8 days followed the exposure period. The bioconcentration factor (BCF) was < 3 adjusted to a 5% lipid content (Klimisch 1, reliable without restriction).
- Based on the weight of evidence, a score of Very Low was assigned. Although the experimental log K_{ow} corresponds to a Very High score, ToxServices relied on predicted BAF for this endpoint, as the

EPISuite program takes metabolism, which reduces the bioaccumulation potential, into consideration when estimating BAF. In addition, BCF/BAF is the more reliable measure of true bioaccumulation compared to log K_{ow}, which is just a physicochemical property of the chemical that impacts bioaccumulation potential. This is supported by the measured BCF value of < 5 for a strong surrogate, which is below the GreenScreen® Guidance value of 100 for a Very Low score.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
DPHP was assigned a score of Low for reactivity based on its NFPA physical hazard rating of 0. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when data indicate that they are not GHS classified for any of the reactivity sub-endpoints (CPA 2018b). The confidence in the score is low due to a lack of experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of DPHP. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, DPHP is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix F).
  - Based on the structure of its components or moieties, DPHP is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.
- BASF 2015
  - A safety data sheet for DPHP reports it has a Reactivity rating of 0 form NFPA ("Materials that are stable even under exposure to fire") [10] and a physical hazard rating 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").

Flammability (F) Score (vH, H, M, or L): L
DPHP assigned a score of Low for flammability based on its flash point of 220°C, and not being classified as a flammable liquid. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on a measured flashpoint for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2022a
  - DPHP had a flash point of 220°C in a Pensky-Martens closed cup assay (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Low was assigned. GHS criteria state that liquids are not classified as flammable is the flash point is greater than 93°C (UN 2021).

[10] https://www.fm.colostate.edu/files/forms/safety/CH-23.NFPA.ratings.pdf

Use of New Approach Methodologies (NAMs)[11] in the Assessment, Including Uncertainty Analyses of Input and Output

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

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

As shown in Table 4, Type I (input data) uncertainties in DPHP's NAMs dataset include the absence of experimental data for respiratory sensitization, and environmental partitioning, and lack of established test methods for respiratory sensitization. DPHP's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays to mimic *in vivo* metabolic conditions, lack of defined applicability domains for OECD Toolbox and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of the type I and type II errors can be alleviated by the use of genotoxicity test batteries in combination with *in vivo* data, and ECHA's decision framework to evaluate respiratory sensitization.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Genotoxicity:** No Type I uncertainty is identified on using the *in vitro* genotoxicity assays as they are considered relevant (appropriate for the evaluation of the corresponding hazards as recommended in the OECD Guideline), reliable (they have Klimisch scoring of 2 or 1) and adequate (validated methods). **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Persistence:** No environmental partitioning data were identified.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[12]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo*

[11] 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).
[12] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

	metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[13] The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[14]. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity		
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	N	
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD Guideline 301B CO2 Evolution Test.
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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

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United States Environmental Protection Agency (U.S. EPA). 2020. New Approach Methods Workplan. Office of Research and Development. Office of Chemical Safety and Pollution Prevention. EPA 615B20001. June 2020. Available: https://www.epa.gov/sites/production/files/2020-06/documents/epa_nam_work_plan.pdf

United States Environmental Protection Agency (U.S. EPA). 2021. Safer Chemical Ingredients List (SCIL). Available: https://www.epa.gov/saferchoice/safer-ingredients

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 DPHP (CAS #53306-54-0)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	**DPHP**	**53306-54-0**	DG	**L**	**L**	*M*	*M*	**L**	**L**	*M*	*L*	DG	**L**	*L*	**L**	**L**	**L**	**L**	**vL**	**vL**	*L*	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
DPHP	2

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

Table 6

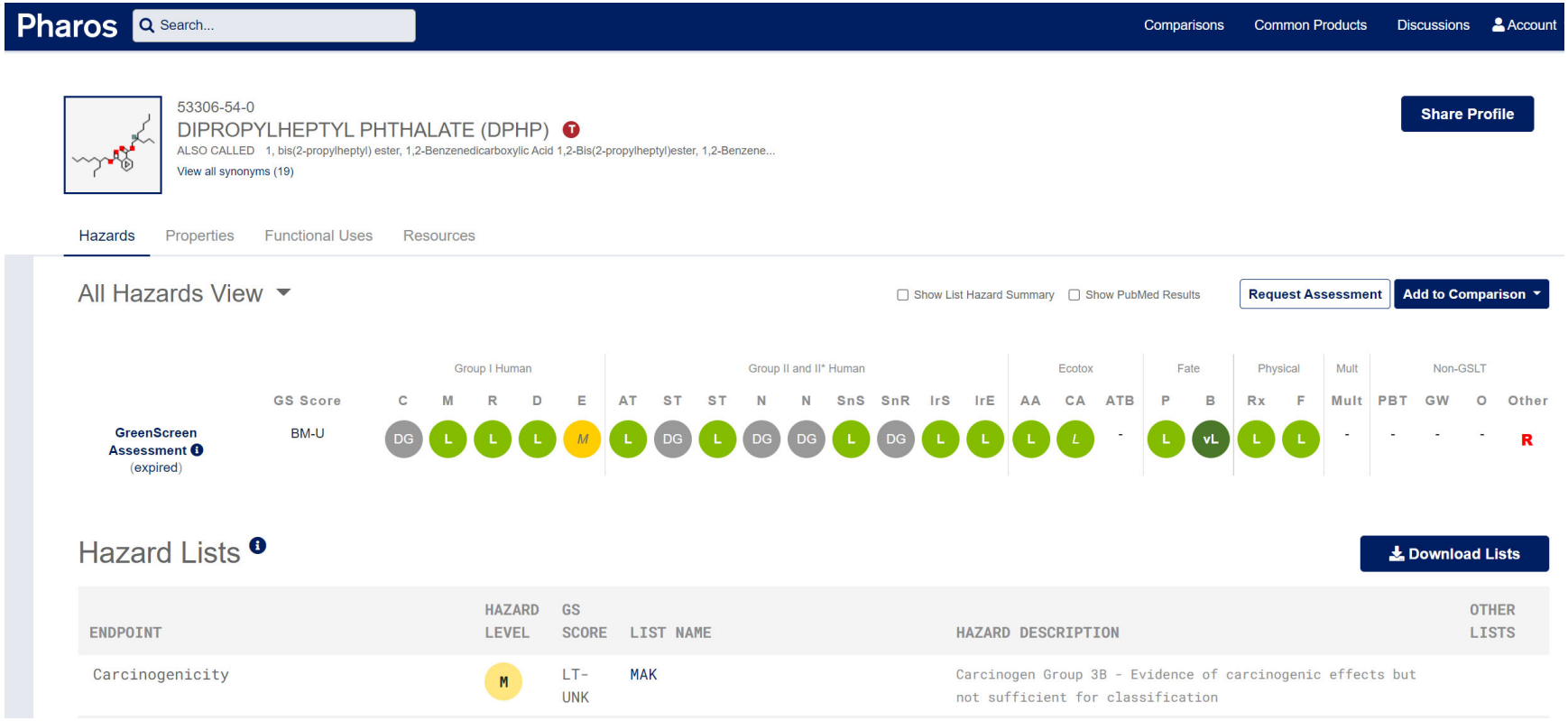
Chemical Name	Final GreenScreen® Benchmark Score
DPHP	U

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

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	No	Yes	Yes	Yes	Yes							U
3												
4												

APPENDIX C: Pharos Output for DPHP (CAS #53306-54-0)



Reproductive Toxicity	pC	NoGS	DK-EPA - Danish Advisory List	Repr. 2; H361 - Suspected of damaging fertility or the unborn child (modeled)	
Endocrine Activity	pC	NoGS	ECHA Endocrine Disruptors	ECHA Endocrine disruptor assessment list	+1
	pC	NoGS	Endocrine Disruptor Lists (Danish EPA)	ED List II - Substances under evaluation for endocrine disruption under an EU legislation	
Respiratory Sensitization	M	NoGS	CHE - Toxicant Database	Asthma - allergen, sensitizer - limited evidence *	+2
	M	NoGS	CHE - Toxicant Database	Asthma - irritant - limited evidence *	
	M	NoGS	CHE - Toxicant Database	Rhinitis – allergic - limited evidence *	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

Restricted Substance Lists (16)

- American Apparel and Footwear Association Restricted Substance List (AAFA RSL): Phthalates *
- CA DTSC - Biomonitoring California Chemical List: Priority Chemical *
- CA SCP - Candidate Chemicals: Candidate Chemical List
- Credo Beauty's Restricted Substance List: Prohibited Chemicals *
- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- Food Contact Chemicals Database (FCCdb): Food Contact Chemicals Database Version 5.0
- GreenScreen Certified Standard for Food Service Ware: Ortho-Phthalates
- GSPI - Six Classes of Problematic Chemicals: Bisphenols and Phthalates *
- Living Building Challenge 2.1 - Red List of Materials & Chemicals: Red List substance to avoid in Living Building Challenge V2.1 projects *
- Living Building Challenge 4.0 - Red List of Materials & Chemicals: Red List substances to avoid in Living Building Challenge V4.0 projects
- Living Future - Living Building Red List 3.0: Prospective Red List substances to avoid in Living Building Challenge projects *
- Living Future - Living Building Red List 3.0: Red List substances to avoid in Living Building Challenge V3 projects
- Living Future - Living Building Red List 3.1: Red List substances to avoid in Living Building Challenge V3.1 projects
- P&W - Precautionary List: Precautionary list of substances recommended for avoidance *
- USGBC - LEED Pilot Credits: Substance to avoid to fulfill LEED Pilot Credit 11 *
- USGBC - LEED Pilot Credits: Substance to avoid to fulfill LEED Pilot Credit 54 Option 2 *

Positive Lists (1)

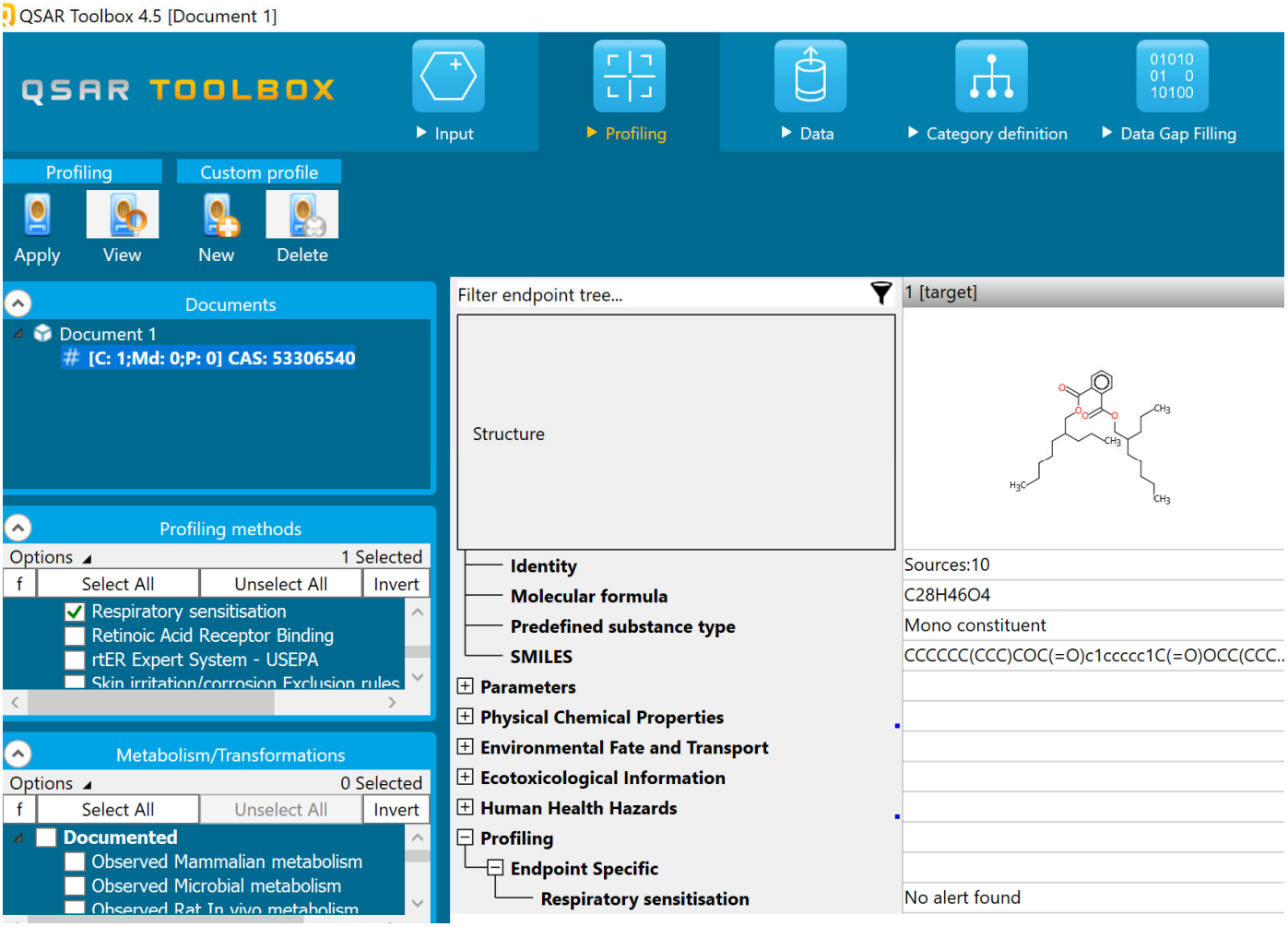
- TCO Certified potential candidate list (tentative - awaiting assessment): TCO Certified potential candidate list (tentative - awaiting assessment)

Discussions

No discussions have been posted yet.

Ask a question about this chemical in the forums >

APPENDIX D: OECD Toolbox Respiratory Sensitization Results for DPHP (CAS #53306-54-0)



APPENDIX E: EPI Suite™ Modeling Results for DPHP (CAS #53306-54-0)

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

CAS Number: 053306-54-0
SMILES : O=C(OCC(CCCCC)CCC)c(c(ccc1)C(=O)OCC(CCCCC)CCC)c1
CHEM : Di(2-propylheptyl) phthalate
MOL FOR: C28 H46 O4
MOL WT : 446.68
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : -48.00
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 10.36

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 463.36 (Adapted Stein & Brown method)
Melting Pt (deg C): 105.95 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 2.29E-007 (Modified Grain method)
VP (Pa, 25 deg C) : 3.05E-005 (Modified Grain method)
MP (exp database): -48 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 9.965e-006
log Kow used: 10.36 (estimated)
melt pt used: -48.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 1.039e-005 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 3.67E-005 atm-m3/mole (3.72E+000 Pa-m3/mole)
Group Method: 4.06E-005 atm-m3/mole (4.11E+000 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.351E-002 atm-m3/mole (1.369E+003 Pa-m3/mole)
VP: 2.29E-007 mm Hg (source: MPBPVP)
WS: 9.97E-006 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 10.36 (KowWin est)
Log Kaw used: -2.824 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 13.184
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.1001
Biowin2 (Non-Linear Model) : 0.9998
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.0892 (weeks)
Biowin4 (Primary Survey Model) : 4.1994 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.7028
Biowin6 (MITI Non-Linear Model): 0.7039
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.1235
Ready Biodegradability Prediction: YES

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 3.05E-005 Pa (2.29E-007 mm Hg)
Log Koa (Koawin est): 13.184
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.0983
Octanol/air (Koa) model: 3.75
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.78
Mackay model : 0.887
Octanol/air (Koa) model: 0.997

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 27.6076 E-12 cm3/molecule-sec
Half-Life = 0.387 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 4.649 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.834 (Junge-Pankow, Mackay avg)
0.997 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1.319E+006 L/kg (MCI method)
Log Koc: 6.120 (MCI method)

Koc : 3.345E+006 L/kg (Kow method)
Log Koc: 6.524 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 4.117E-002 L/mol-sec
Kb Half-Life at pH 8: 194.873 days
Kb Half-Life at pH 7: 5.335 years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.883 (BCF = 76.38 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.6220 days (HL = 4.187 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.099 (BCF = 1.256)
Log BAF Arnot-Gobas method (upper trophic) = 1.123 (BAF = 13.27)
log Kow used: 10.36 (estimated)

Volatilization from Water:
Henry LC: 4.06E-005 atm-m3/mole (estimated by Group SAR Method)
Half-Life from Model River: 32.63 hours (1.36 days)
Half-Life from Model Lake : 533.2 hours (22.22 days)

Removal In Wastewater Treatment:
Total removal: 94.04 percent
Total biodegradation: 0.78 percent
Total sludge adsorption: 93.26 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)
** Note: When the Log Kow is > 7, the model may be underestimating the mass of material in sediment and overestimating the mass of material in the water column (biota). Consider using the results of the default EQC model. **

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.571	9.3	1000
Water	21.6	360	1000
Soil	77.1	720	1000
Sediment	0.733	3.24e+003	0

Persistence Time: 538 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.571	9.3	1000
Water	21.6	360	1000
water	(0.0188)		
biota	(21.5)		

suspended sediment (0.0372)
Soil 77.1 720 1000
Sediment 0.733 3.24e+003 0
Persistence Time: 538 hr

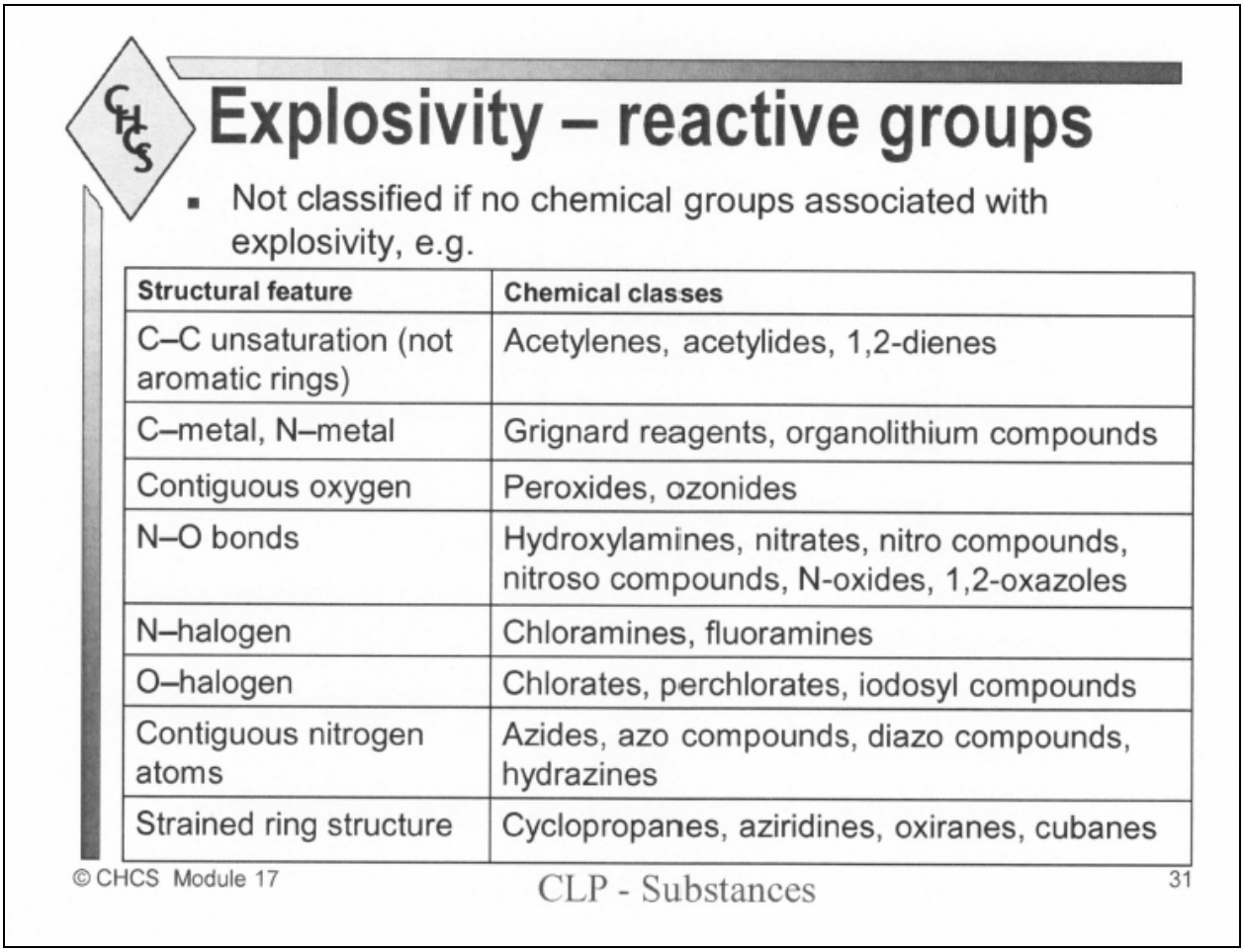
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**0.231**	**9.3**	**1000**
Water	**3.57**	**360**	**1000**
water	**(0.000234)**		
biota	**(0.268)**		
suspended sediment	**(3.3)**		
Soil	**31.2**	**720**	**1000**
Sediment	**65**	**3.24e+003**	**0**

Persistence Time: 1.33e+003 hr

APPENDIX F: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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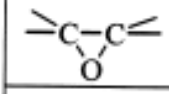
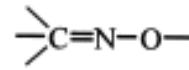
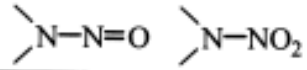
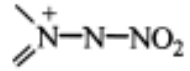
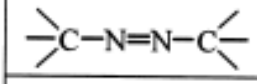
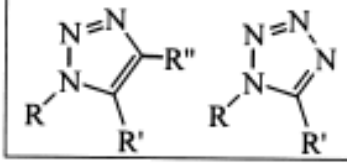
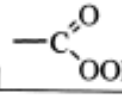
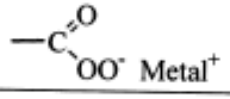
Explosivity – Full List

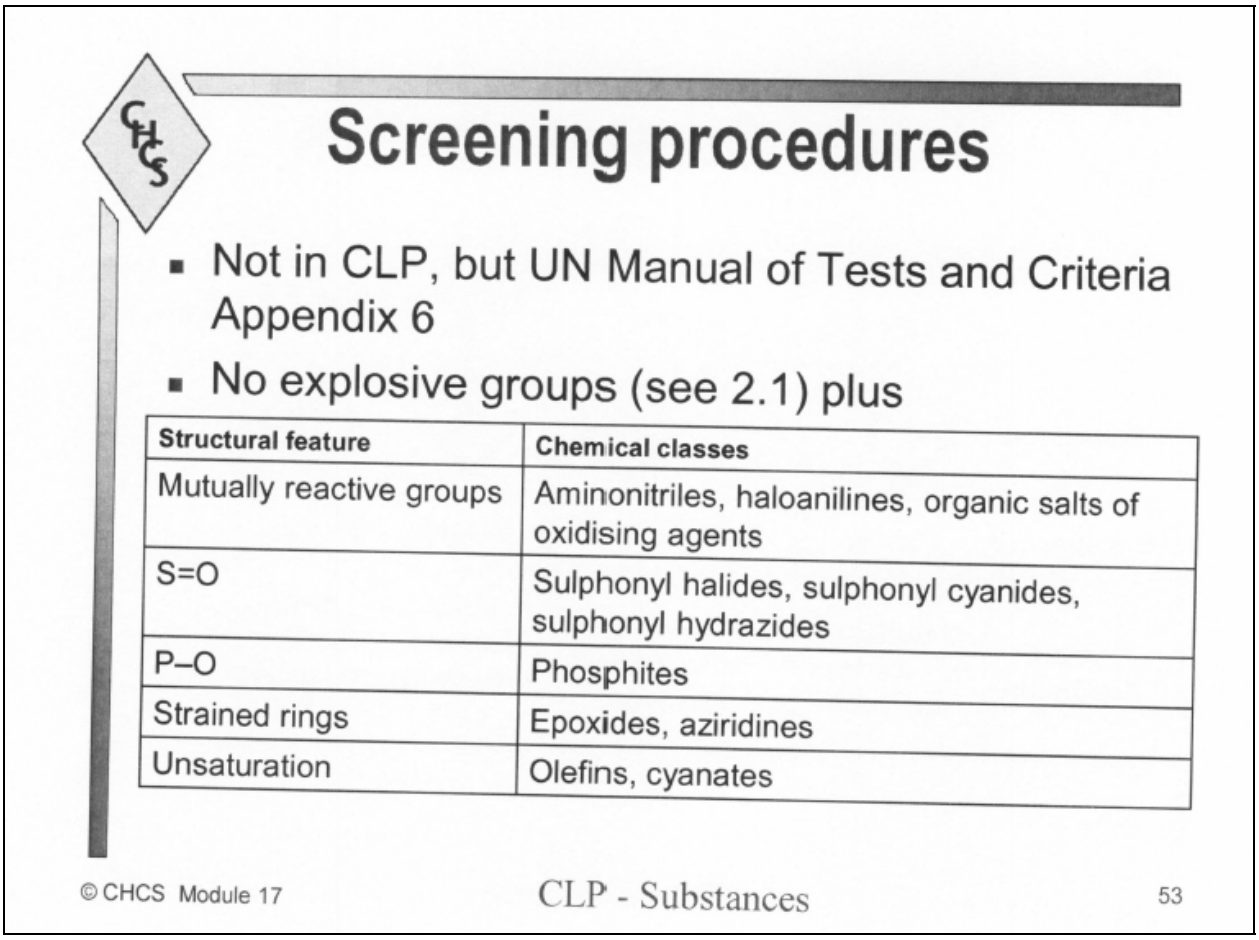
Table R.7.1-28 Chemical groups associated with explosive properties

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

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

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

Self-Reactive Substances



Screening procedures

- Not in CLP, but UN Manual of Tests and Criteria Appendix 6
- No explosive groups (see 2.1) plus

Structural feature	Chemical classes
Mutually reactive groups	Aminonitriles, haloanilines, organic salts of oxidising agents
S=O	Sulphonyl halides, sulphonyl cyanides, sulphonyl hydrazides
P–O	Phosphites
Strained rings	Epoxides, aziridines
Unsaturation	Olefins, cyanates

APPENDIX G: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for DPHP. The GreenScreen® Benchmark Score for DPHP has changed over time. The original GreenScreen® assessment was performed in 2012 under version 1.2 criteria and ToxServices assigned a Benchmark U (BM-U) score. The BM-U score was changed with a version 1.3 update in 2018. Most recently, ToxServices changed the GreenScreen® benchmark score to a BM-U due to reclassification of the carcinogenicity endpoint from *M* (low confidence) to DG following a weight of evidence evaluation of this chemical's carcinogenicity dataset.

Table 5: Change in GreenScreen® Benchmark™ for DPHP

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
May 30, 2012	BM-U	v. 1.2	
February 9, 2018	BM-2	v. 1.3	BM score changed to a BM-2 due to reclassification of carcinogenicity and respiratory sensitization endpoints from DG to *Moderate* (low confidence) and *Low* (low confidence), respectively.
March 15. 2022	BM-U	v. 1.4	BM score changed to a BM-U due to reclassification of carcinogenicity endpoint from *Moderate* (low confidence) to DG.

Licensed GreenScreen® Profilers

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