DI(2-ETHYLHEXYL) TEREPHTHALATE (DEHT)

(CAS #6422-86-2)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: January 12, 2021

Expiration Date: January 12, 2026

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

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GreenScreen® Executive Summary for Di(2-ethylhexyl) Terephthalate (DEHT) (CAS #6422-86-2)

Di(2-ethylhexyl) terephthalate (DEHT) is a clear, non-flammable liquid that functions as a plasticizer for polyvinyl chloride (PVC) with applications including wire and cable coatings, pond liners, shoe soles, gaskets for bottle caps and enclosures, flooring products, weather-stripping, and water-proof fabric coatings. DEHT is not considered to be a part of the common "phthalate ester" class, because it is not ortho-substituted. DEHT is a 1,4-benzenedicarboxylic isomer (para position=terephthalic acid), while the ortho-phthalate di(2-ethylhexyl)phthalate is a 1,2-benzenedicarboxylic acid (para position = phthalic acid), where each are esterified with 2-ethylhexanol.

DEHT was assigned a **GreenScreen Benchmark™ Score of 3_{DG}** ("Use but Still Opportunity for Improvement due to Data Gaps"). Prior to data gap analysis, it was assigned a preliminary benchmark score of 4. This score is based on the following hazard score combinations:

- Benchmark 4
  - Low Group I Human Toxicity (carcinogenicity-C, mutagenicity-M, reproductive toxicity-R, and developmental toxicity-D)
  - Low Group II Human Toxicity (acute toxicity-AT, single exposure systemic toxicity-STs, single exposure neurotoxicity-Ns, skin irritation-IrS, and eye irritation-IrE)
  - Low Group II* Human Toxicity (repeated exposure systemic toxicity-STr*, skin sensitization-SnS*, and respiratory sensitization-SnR*)
  - Low Ecotoxicity (acute aquatic-AA and chronic aquatic-CA)
  - Very Low Persistence-P
  - Low Bioaccumulation-B
  - Low Physical Hazards (reactivity-Rx and flammability-F)

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), DEHT does not meet the requirements for a GreenScreen® Benchmark Score of 4 due to the hazard data gaps. However, it meets the criteria for a Benchmark Score of 3. In a worst-case scenario, if DEHT were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Hazard Summary Table for DEHT

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
						single	repeat*	single	repeat*										
L	**L**	**L**	*L*	DG	**L**	**L**	**L**	*L*	DG	**L**	*L*	**L**	**L**	**L**	**L**	**vL**	**L**	*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 Di(2-ethylhexyl) Terephthalate (DEHT) (CAS #6422-86-2)

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

GreenScreen® Assessment (v1.2) Prepared By:
Name: Chris Schlosser, M.F.S.
Title: Associate Toxicologist
Organization: ToxServices, LLC
Date: February 27, 2012

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: February 29, 2012

GreenScreen® Assessment (v1.2) Updated By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 21, 2015

Quality Control Performed By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Toxicologist
Organization: ToxServices, LLC
Date: October 30, 2015

GreenScreen® Assessment (v1.3) Updated By:
Name: Lindsey Lund, M.S.
Title: Associate Toxicologist
Organization: ToxServices LLC
Date: August 18, 2016

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: September 20, 2016, May 16, 2017

GreenScreen® Assessment (v1.4) Updated By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: May 7, 2018

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 10, 2018

GreenScreen® Assessment (v1.4) Updated By:
Name: Megan Boylan, M.S.
Title: Toxicologist
Organization: ToxServices LLC
Date: September 6, 2019

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: September 9, 2019

GreenScreen® Assessment (v1.4) Updated By:
Name: Sara Ciotti, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: January 8, 2021

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: January 12, 2021

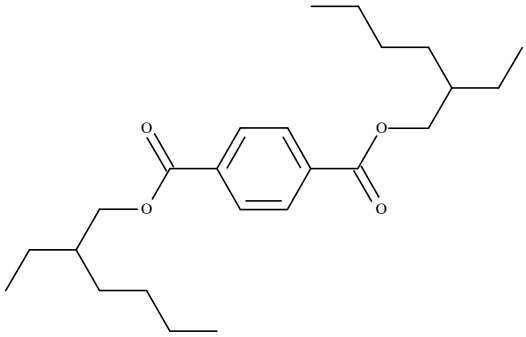
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).

Expiration Date: January 11, 2026[2]

Chemical Name: Di(2-ethylhexyl) terephthalate (DEHT)

CAS Number: 6422-86-2

Chemical Structure(s):



Also called: bis(2-Ethylhexyl)terephthalate; 1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester; Terephthalic acid, bis(2-ethylhexyl) ester; 1,4-Benzenedicarboxylic acid, 1,4-bis(2-ethylhexyl) ester (ChemIDplus 2021); Dioctyl terephthalate (DOTP) (UNEP 2003)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
DEHT has a relatively complete toxicological dataset. For endocrine activity and repeated dose neurotoxicity, no appropriate surrogates with data available were identified. Therefore, a Data Gap was assigned for each endpoint lacking data.

Identify Applications/Functional Uses:
DEHT is used as a plasticizer for PVC (wire and cable coatings, pond liners, shoe soles, gaskets for bottle caps and enclosures, flooring products, weather-stripping, and water-proof fabric coatings) (UNEP 2003).

Known Impurities[3]:
DEHT is manufactured at >98% purity. One impurity present at < 2% is reported to be 2-ethylhexyl methyl terephthalate (CAS #63468-13-3) (UNEP 2003). 2-Ethylhexyl methyl terephthalate is an LT-U ("GreenScreen List Translator (LT) Unknown Chemical") chemical (Pharos 2021). GreenScreen® Guidance requires a full GreenScreen® for each impurity present at ≥ 100 ppm, and a List Translator screening for impurities present at < 100 ppm (CPA 2018b).

As this GreenScreen® is performed on generic DEHT, information on impurities is not available and the screen is performed on the theoretical pure substance.

[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).
[3] Potential impurities of DEHT are not assessed in this GreenScreen®.

GreenScreen® Summary Rating for DEHT[4,5 6,7]: DEHT was assigned a **GreenScreen Benchmark™ Score of 3_{DG}** ("Use but Still Opportunity for Improvement due to Data Gaps") (CPA 2018b). Prior to data gap analysis, it was assigned a preliminary benchmark score of 4. This score is based on the following hazard score combinations:

- Benchmark 4
  - Low Group I Human Toxicity (carcinogenicity-C, mutagenicity-M, reproductive toxicity-R, and developmental toxicity-D)
  - Low Group II Human Toxicity (acute toxicity-AT, single exposure systemic toxicity-STs, single exposure neurotoxicity-Ns, skin irritation-IrS, and eye irritation-IrE)
  - Low Group II* Human Toxicity (repeated exposure systemic toxicity-STr*, skin sensitization-SnS*, and respiratory sensitization-SnR*)
  - Low Ecotoxicity (acute aquatic-AA and chronic aquatic-CA)
  - Very Low Persistence-P
  - Low Bioaccumulation-B
  - Low Physical Hazards (reactivity-Rx and flammability-F)

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), DEHT does not meet the requirements for a GreenScreen® Benchmark Score of 4 due to the hazard data gaps. However, it meets the criteria for a Benchmark Score of 3. In a worst-case scenario, if DEHT were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for DEHT

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
						single	repeat*	single	repeat*										
L	L	L	*L*	DG	L	L	L	*L*	DG	L	*L*	L	L	L	L	vL	L	*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:

Although DEHT is an ester with a potential for hydrolysis reactions, a preliminary hydrolysis test indicates that little, if any, hydrolysis occurs even at 50ºC at the pH range of 4-9 (ECHA 2021). Biodegradation studies on DEHT reported that it is readily biodegradable (ECHA 2021). Therefore, it is not expected to produce any environmental transformation products that are persistent enough to be relevant to this assessment.

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

Introduction

DEHT is an ortho-phthalate alternative. DEHT is not considered to be a part of the common "phthalate ester" class, as it is not ortho-substituted. DEHT is compatible with use in cellulose acetate-butyrate, cellulose nitrate, polymethyl methacrylate, polystyrene, polyvinyl butyral, and PVC resins (CPSC 2010). DEHT is manufactured by combining terephthalic acid with 2-ethylhexanol followed by purification via distillation (UNEP 2003).

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

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2020a). 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).

DEHT is not listed on the SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2018b). Pharos (2021) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for DEHT can be found in Appendix C.

- DEHT appears in Pharos as a Benchmark 3_{DG} chemical based on an expired version 1.3 GreenScreen® completed by ToxServices in 2016. This current GreenScreen® brings the assessment up to date.
- DEHT is on the following list for multiple endpoints. It is not present on any GreenScreen®-specified lists for single endpoints.
    - EC CEPA DSL – Inherently Toxic in the Environment (iTE)

Hazard Statement and Occupational Control

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

Table 1: GHS H Statements for DEHT (CAS #6422-86-2) (ECHA 2021)

GHS 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.	

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

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for DEHT (CAS #6422-86-2)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Good ventilation should be used and respiratory and eye protection may be needed in special circumstances. It is good industrial hygiene practice to minimize eye contact and skin contact.	ECHA 2021	Not established	UNEP 2003

Physicochemical Properties of DEHT

DEHT is a clear liquid at room temperature. It has a low vapor pressure, indicating a low potential to form a vapor. DEHT has negligible water solubility, and the predicted partition coefficients suggest that it is not readily bioavailable.

Table 3: Physical and Chemical Properties of DEHT (CAS #6422-86-2)		
Property	**Value**	**Reference**
Molecular formula	$C_{24}H_{38}O_4$	ChemIDplus 2021
SMILES Notation	c1(C(=O)OCC(CCCC)CC)ccc(cc1)C(=O)OCC(CCCC)CC	ChemIDplus 2021
Molecular weight	390.5602 g/mol	ChemIDplus 2021
Physical state	Liquid	UNEP 2003
Appearance	Clear	UNEP 2003
Melting point	-48ºC	UNEP 2003
Boiling point	375°C (EU Method A.2)	ECHA 2021
Vapor pressure	<0.001 Pa at 25ºC (EU Method A.4) 2.5 x 10^{-6} mmHg at 25°C (est.)	ECHA 2021 U.S. EPA 2017
Water solubility	0.0004 mg/L at 22.5ºC	UNEP 2003
Dissociation constant	NA	
Density/specific gravity	0.98 g/cm^3 at 20ºC (EU Method A.3)	ECHA 2021
Partition coefficient	log K_{ow} = 8.39 (est.)	U.S. EPA 2017

Toxicokinetics

DEHT is not readily absorbed through the skin. After oral ingestion, 36.6% of DEHT is excreted unchanged in the feces. The majority of the remaining DEHT is primarily metabolized by hydrolysis into terephthalic acid (TPA) and excreted in the feces and urine, with lesser amount eliminated in expired air (3.6%). DEHT has a low potential for bioaccumulation.

- ECHA 2021
    - In a GLP-compliant study in CD COBS rats, radiolabeled DEHT ([hexyl-2-^{14}C]di(2-ethylhexyl) terephthalate (specific activity 8.39 mCi/mmole) was mixed with non-labeled DEHT and dissolved in corn oil. Each rat received a single dose of 100 mg/kg test substance by oral gavage. Mean total recovery of ^{14}C was 93 $\pm$ 2.2%. Most of the radioactivity was eliminated in the feces and urine, 56.5% and 31.9%, respectively, with 3.6% eliminated in expired air. Study investigators approximated 1.4% of the dose remained in the carcass. The majority of the recovered dose (>95%) was excreted within 24 hours. In the feces, 36.6% of the total dose was unchanged DEHT. 50.5% of the total dose recovered in the urine was TPA. Metabolite analysis indicated that the major excretory

products of DEHT are (TPA and DEHT, together accounting for 87.1% of the dose. Only a small percentage of the administered dose was excreted as mono-(2-ethylhexyl) terephthalate or its oxidative metabolites. Under the conditions of the study, study investigators concluded DEHT has a low potential for bioaccumulation and presents a low toxicity hazard. This study was assigned a Klimisch score of 2 (reliable with restrictions).

- Percutaneous absorption of DEHT was measured in a GLP-compliant study conducted according to OECD Guideline 423 using dermatomed sections of human skin at a rate of 0.103 µg/cm^2. The damage ratio was calculated from the rates of tritiated water before and after DEHT exposure and was similar to the negative control indicating that exposure to DEHT for 29 hours does not significantly damage the skin. Study investigators estimated 1.06 µg/kg DEHT uptake occurs following a continuous 1-hour dermal exposure in an area of skin equivalent to both hands (approximately 720 cm^2, 70-kg person). This study was assigned a Klimisch score of 1 (reliable without restriction).

Hazard Classification Summary:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): L
DEHT was assigned a score of Low for carcinogenicity based on a lack of evidence of carcinogenic effects or statistically significant increases in tumors in a 2-year carcinogenicity assay in rats. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on a well-conducted animal study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Deyo 2008, ECHA 2021
  - A GLP-compliant 104-week chronic toxicity/carcinogenicity study (EPA OPPTS 870.4200) was conducted using male and female Fischer 344 rats (50/sex/dose). Rats were administered DEHT at doses of 0, 79, 324, and 666 mg/kg in males and 0, 102, 418, and 901 mg/kg (> 98% purity) in females daily in the diet. There was no evidence of a treatment-related effect on the incidence of any tumor type for any group of rats. There were no statistically significant dose-related differences in incidences of specific tumors between treated and control groups. Toxic responses were limited to reduced body weight gain and food conversion efficiency in the top two dose groups. This study was assigned a Klimisch score of 1 (reliable without restriction).

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L
DEHT was assigned a score of Low for mutagenicity/genotoxicity based on negative *in vitro* mutagenicity and clastogenicity assays. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on high quality data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

- Barber 1994
    - A non-GLP compliant bacterial reverse mutation assay (method not reported) was conducted utilizing *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of up to 10,000 µg/plate with and without metabolic activation. No mutagenic activity was identified under the tested conditions and DEHT was reported as negative for mutagenicity.
    - A GLP compliant HGPRT assay (similar to OECD Guideline 476) was conducted utilizing CHO cells at concentrations of up to 20 nL/mL with and without metabolic activation. No statistically significant increases in mutation frequencies were reported when compared to controls. DEHT was reported as negative for mutagenicity under the tested conditions.
    - A GLP compliant chromosomal aberration assay (similar to OECD Guideline 473) was conducted utilizing Chinese hamster ovary (CHO) cells at concentrations up to 1,000 nL/mL with and without metabolic activation. No increases in aberrations were identified and DEHT was reported as negative for clastogenicity.
- ECHA 2021
    - A bacterial reverse mutation assay (GLP status not reported) was conducted in a manner similar to OECD Guideline 471. The tested material was pooled urine from male Sprague-Dawley rats exposed via gavage to DEHT (purity not reported) at 2,000 mg/kg/day daily for 15 days. The test procedure was modified so that both the glucuronide and sulfate conjugates can be hydrolyzed and possibly metabolized by S9 to improve the sensitivity of the assay. *S. typhimurium* test strains TA98, TA100, TA1535, and TA1538 were exposed to 0.02-2 mL urine per plate in the presence and absence of metabolic activation. The test substance was determined to be non-mutagenic. Both positive and negative controls are valid.

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

DEHT was assigned a score of Low for reproductive toxicity based on a lack of effects on reproductive parameters in a 2-generation (OECD Guideline 416) reproductive toxicity study. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on a well-conducted study.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists
- Faber et al. 2007a, ECHA 2021
    - A GLP compliant 2-generation reproductive toxicity study (OECD Guideline 416) was conducted using male and female Sprague-Dawley rats (30/sex/dose). Rats were administered doses of 0, 0.3, 0.6, and 1.0% of DEHT (97.1% purity) in the diet from 70 days pre-mating to termination in the F0 generation and from postnatal day (PND 22) until termination in the F1 generation. Reproductive parameters (fertility, mating, days between pairing and coitus, gestation, parturition, and estrous cycling), mean litter sizes, numbers of pups born, percentages of males per litter at birth and postnatal survival were unaffected. Female rats displayed systemic toxicity in the 0.6% and 1.0% groups as reflected by decreased food consumption. Slight decreases in organ weights in the top dose F1 group were considered to be secondary to maternal toxicity. Additionally, no dose-response could be established. Based on available data, a reproductive NOEL of 1.0% (reported to be equivalent to 614 mg/kg/day (Faber et al. 2007a)) was established by study authors based on the absence of adverse reproductive effects. Additionally, a parental systemic NOEL of

0.3% (reported to be equivalent to 182 mg/kg/day (Faber et al. 2007a)) was identified based on reduced body weight in F1 males, increased mean absolute (F0 females) and mean relative (F0 and F1 females) liver weights at 0.6%. This study was assigned a Klimisch score of 1 (reliable without restriction).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
DEHT was assigned a score of Low for developmental toxicity based on the absence of specific fetal toxicity or teratogenicity in three developmental toxicity studies in rats and mice. The only effect observed was statistically significant reduction in pup body weight reported in the presence of maternal toxicity in a two-generation toxicity study. ToxServices derived a $BMDL_{05}$ of 197 mg/kg/day for this effect (Appendix E). However, other developmental toxicity studies did not report similar effects at doses of > 700 mg/kg/day even at doses that caused maternal toxicity. The overall weight of evidence suggests that this effect is likely attributed to maternal toxicity, as suggested by the study authors. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low due to the uncertainty regarding reduced fetal body weight only in the presence of maternal toxicity in one study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Faber et al. 2007b
  - A GLP compliant developmental toxicity study (OECD Guideline 414) with uterotrophic evaluations was conducted using female Sprague-Dawley rats (25/group). Rats were administered doses of 0, 229, 458, and 747 mg/kg (purity not reported) of the test substance on gestation days (GD) 0-20. In the uterotrophic examinations sexually immature rats were administered doses of 20, 200, and 2,000 mg/kg via oral gavage on PNDs 19 to 21. Number of viable and non-viable fetuses, resorptions and implantation sites, and corpora lutea did not differ from controls. No visceral or skeletal anomalies and no signs of developmental toxicity were reported. In the uterotrophic assay for estrogenic activity DEHT exposure did not affect wet or blotted uterine weight parameters. A NOAEL of 747 mg/kg for developmental toxicity was established by the study authors.
  - A GLP compliant developmental toxicity study (OECD Guideline 414) was conducted using female CD-1 mice (25/group). Mice were administered doses of 0, 197, 592, and 1,382 mg/kg of DEHT (≥ 97.6%) in the diet on GD 0-18. No effects were observed on the number of malformations/skeletal variations, litter size, fetal body weights or sex ratios. No evidence of fetotoxicity or teratogenicity was observed even at maternally toxic doses. A NOEL of 1,382 mg/kg was identified for developmental toxicity by the authors.
- Faber et al. 2007a
  - In a previously-described GLP-compliant 2-generation reproductive toxicity study (OECD Guideline 416), Sprague-Dawley rats (30/sex/dose) were administered doses of 0, 0.3, 0.6, and 1.0% of DEHT (97.1% purity) in the diet from 70 days pre-mating to termination in the F0 generation and from PND 22 until termination in the F1 generation. Mean litter sizes, numbers of pups born, percentages of males per litter at birth and postnatal survival were unaffected. Female rats displayed systemic toxicity in the mid and high dose groups as reflected by decreased food consumption. Slight decreases in organ weights in the top dose F1 group were considered to be secondary to maternal toxicity. Statistically significant decreases in pup body weight were reported in F1 animals on PND1 and PND 21 in both sexes at the mid and high doses, in F2 animals on PND1 in both sexes at the high dose, and

in F2 animals on PND21 in both sexes at the mid and high doses. The decrease in body weight appears to be dose-dependent, although no statistical tests were performed. *ToxServices performed Benchmark Dose Modeling and determined BMD_{05} and $BMDL_{05}$ of 284 and 197 mg/kg/day, respectively (Appendix E).*

- ECHA 2021
  - A (GLP status not reported) developmental toxicity limit test (method not reported) was conducted using female Sprague-Dawley rats (number not reported). Rats were administered doses of 0 or 750 mg/kg of DEHT (98% purity) on GD 14 through PND 3 via gavage. No maternal toxicity, fetotoxicity, or teratogenicity was reported at any dose level. A NOEL of 750 mg/kg was reported by the study authors. This study was assigned a Klimisch score of 1 (reliable without restriction).
- Liu et al. 2005
  - An additional study was performed to investigate the gene expression in the fetal testis following *in utero* exposure to DEHT. While this not a standard guideline study and is not applicable to the GreenScreen® scoring criteria, it does provide insight into the mechanistic nature and mode of action of phthalates on testicular effects. In this study it was found that DEHT did not alter gene expression following *in utero* exposure on GD 12-19.

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

DEHT was assigned a score of Data Gap for endocrine activity based on the harmonized hazard score assigned by an external expert committee assembled by CPA supported by a lack of adequate data for all of the endocrine pathways. Sufficient data have been provided to demonstrate that DEHT does not show evidence of estrogenic or androgenic activity. Although no thyroid effects were observed, limited data were available to fully assess potential thyroid effects of DEHT, and ToxServices did not consider the negative high throughput data alone to be sufficient to assign a Low.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Gray et al. 2000
  - DEHT was tested for its potential to alter sexual differentiation of the male rat following perinatal exposure. DEHT was orally administered to pregnant dams from GD 14 to PND 3. Study results indicated that DEHT did not induce overt maternal toxicity or reduced litter sizes. No changes were observed in anogenital distance, testis weights, or nipple retention. Study authors concluded that DEHT was ineffective at 750 mg/kg at altering sexual differentiation in male rats. A slight decrease in serum testosterone was reported, but did not reach statistical significance. Spermatogenic assessment conducted during the 2-generation reproductive toxicity study appeared normal (Faber et al. 2007a). A slight decrease in serum testosterone was reported, but did not reach statistical significance. However, the lack of effects on reproductive organ weights in both the current study and the 2-generation study, and lack of effects on the spermatogenic assessment in the 2-generation study indicate that DEHT is unlikely to affect the endocrine activity in male rats. Additionally, the lack of effects on estrogenic activity following the developmental toxicity and uterotrophic assay indicate that DEHT is unlikely to affect endocrine activity in female rats.
- U.S. EPA 2020b
  - DEHT was active in 1/28 estrogen receptor (ER) assays, 0/14 androgen receptor (AR) assays, 0/26 steroidogenesis assays, and 0/10 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century.

- Kambia et al. 2019
    - Kambia et al. studied the endocrine effects of DEHT and its metabolites using level 2 Organization for Economic Co-operation and Development (OECD) bioassays to screen for *in vitro* hormonal changes. While DEHT itself was negative, its hydroxylated monoester metabolite 5-OH-MEHT exhibited ERα agonism, and oxo-derived monoester metabolites were equivalent partial ERα antagonists. 5-OH-MEHT was also an AR agonist. In steroids synthesis assays, MEHT was weakly active and hydroxylated metabolites such as 5-OH-MEHT were more potent, in induction of estradiol synthesis (16 fold by 5-OH-MEHT). MEHT and 5-OH-MEHT also decreased testosterone synthesis. Study authors judged the hormonal activities exerted by DEHT metabolites to be weak, but nevertheless warrant further examination.
- Sheikh et al. 2016
    - An *in silico* approach determined that DEHT fits well into the steroid binding pocket of human sex hormone-binding globulin. The authors concluded that it has the potential for "displacing the endogenous testosterone and estradiol leading to potential disruption of the androgen-estrogen homoeostasis in the body".
- CPA 2017
    - **Endocrine Activity (E) Score (H, M or L):** DATA GAP (Harmonized Score based on Outside Expert Review)
        - To resolve differences in professional opinion among Licensed GreenScreen Profilers over the DEHT endocrine activity hazard score, Clean Production Action convened an expert panel to review the available data pertaining to potential endocrine activity of DEHT. The panel included CPA's consulting toxicologist, as well as experts in endocrine activity from both industry and government. The review process included a telephone meeting during which each Profiler attended (separately) to discuss their approach and rationale used to assign the hazard level. Each outside reviewer was asked to provide to CPA in writing their recommended hazard score and confidence level for Endocrine Activity, based on a review of the data and information provided in each of the GreenScreen Assessments and information from the telephone discussion. Each reviewer was also asked to provide a brief rationale for their conclusion. A member of Clean Production Action's Board of Directors provided oversight throughout the process.
        - The outside reviewers unanimously agreed the Endocrine Activity endpoint should be assigned a DATA GAP based on the available hazard data for DEHT. The reviewers agreed there were insufficient data to support an indication of low hazards for the five endocrine pathways considered within GreenScreen (androgenicity, anti-androgenicity, thyroid effects, estrogenicity, and anti-estrogenicity). Reviewers unanimously agreed there were insufficient data on potential thyroid effects. One reviewer commented much of the data presented to support a low score for endocrine activity were based on general reproductive, developmental toxicity or systemic toxicity tests and that it was unclear from these studies what specific endocrine activity endpoints were observed. Per the reviewer, this is paramount as the lack of a reported effect does not equate to no effect; it is possible an effect is not reported because it was not an observed endpoint in the study. In addition, equating no reproductive effects to no endocrine activity suggests that reproductive or developmental endpoints are the only endpoints affected by endocrine active substances.

- Based on the available data, ToxServices concludes that there is no evidence of estrogenic or androgenic endocrine activity for DEHT in the *in vivo* study in rats. An *in silico* prediction that it fits well into the steroid binding pocket of human sex hormone-binding globulin was not weighed heavily given the lack of effects in an *in vivo* study. However, limited data were available to assess potential thyroid effects of DEHT. GreenScreen® criteria require data demonstrating androgenicity, anti-androgenicity, thyroid effects, estrogenicity, and anti-estrogenicity and require assignment of a Data Gap when data are incomplete for any endocrine mediated pathway (detailed in Appendix D). Although high throughput data do not indicate the potential for thyroid effects, ToxServices does not consider these data sufficient to warrant a score of Low given the absence of *in vivo* data for the thyroid. Therefore, ToxServices has assigned a Data Gap for this endpoint based on a lack of adequate data regarding thyroid activity. This score is consistent with the score unanimously assigned by the CPA external experts (CPA 2017). The only additional data identified since CPA's review are the high throughput data and *in vitro* data published by Kambia et al. suggesting potential steroidogenesis effects by DEHT and more by its metabolites *in vitro*, which are insufficient to justify a change of score.

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

DEHT was assigned a score of Low for acute toxicity based on an oral LD_{50} greater than 3,200 mg/kg and a dermal LD_{50} greater than 5,000 mg/kg. 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 (CPA 2018b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- UNEP 2003, ECHA 2021
  - *Oral*: An oral LD_{50} value of greater than 3,200 mg/kg was identified in male CD-1 mice. This study was assigned a Klimisch score of 2 (reliable with restrictions).
  - *Oral*: An oral LD_{50} value of greater than 3,200 mg/kg was identified in male Sprague-Dawley rats. This study was assigned a Klimisch score of 2 (reliable with restrictions).
  - *Oral*: An oral LD_{50} value of greater than 5,000 mg/kg was identified in CD(SD)BR VAF/Plus rats. This study was assigned a Klimisch score of 1 (reliable without restriction).
  - *Dermal*: A dermal LD_{50} value of greater than 19,670 mg/kg was identified in (strain not reported) guinea pigs. This study was assigned a Klimisch score of 2 (reliable with restrictions).

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

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

DEHT was assigned a score of Low for systemic toxicity (single dose) based on the lack of systemic toxicity in acute toxicity studies after oral and dermal exposure at doses above GHS guidelines. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when there are no systemic effects below the guidance value of 2,000 mg/kg for acute oral and dermal toxicity studies and the chemical is not GHS classified (CPA 2018b). The confidence in the score is high as the score was based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2021
  - *Oral:* In a GLP-compliant acute toxicity study performed according to TSCA FHSA regulations (1979) 16 CFR Part 1500.40, CD(SD)BR VAF/Plus rats (5/sex) received a single dose of neat DEHT (purity not specified) by gavage at 5,000 mg/kg, and were observed for 14 days. No mortalities occurred during the study. Clinical signs were limited to oily, unkempt inguinal hair in all animals on day 1 and 2 only, and yellow discolored inguinal hair in two females on day 1 only. All animals gained weight and there was no treatment-related change upon gross necropsy. Histopathology was not performed. This study was assigned a Klimisch score of 1 (reliable without restriction).
  - *Oral:* In an acute toxicity study that predates GLP, male Sprague-Dawley rats (2/dose) were exposed to DEHT (purity not specified) by gavage at the single dose of 200, 400, 800, 1,600, or 3,200 mg/kg, and were observed for 14 days. No mortalities occurred during the study. There were no clinical signs or altered body weights. Gross pathology was not performed. This study was assigned a Klimisch score of 2 (reliable with restrictions).
  - *Oral:* In an acute toxicity study that predates GLP, male CD-1 mice (2/dose) were exposed to DEHT (purity not specified) by gavage at a single dose of 200, 400, 800, 1,600, or 3,200 mg/kg, and were observed for 14 days. No mortalities occurred during the study. There were no clinical signs or altered body weights. Gross pathology was not performed. This study was assigned a Klimisch score of 2 (reliable with restrictions).
  - *Dermal:* In an acute toxicity study that predates GLP, guinea pigs (1/dose, sex not specified) were exposed to neat DEHT (purity not specified) on the skin under occlusion for 24 hours at a single dose of 5.0, 10.0, or 20.0 mL/kg, and were observed for 14 days. There were no signs of systemic toxicity or dermal absorption. Local irritation was demonstrated by moderate to gross edema at 24 hours and slight desquamation on days 7 and 14. All animals gained weight during the study, and no gross pathology was performed. This study was assigned a Klimisch score of 2 (reliable with restrictions).

Group II* Score (repeated dose) **(ST-repeat) (H, M, or L): L**

DEHT was assigned a score of Low for systemic toxicity (repeated dose) based on oral NOAELs greater than 100 mg/kg/day in subchronic and chronic studies. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when there are no systemic effects below the guidance value of 100 mg/kg for 90-day oral and dermal toxicity studies and the chemical is not GHS classified (CPA 2018b). The confidence in the score is high because it is based on experimental data from well conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Deyo 2008, ECHA 2021
  - *Oral:* A GLP compliant 104-week chronic toxicity/carcinogenicity study (EPA OPPTS 870.4200) was conducted using male and female Fischer 344 rats (50/sex/dose). Rats were administered doses of 0, 79, 324, and 666 mg/kg in males and 0, 102, 418, and 901 mg/kg (> 98% purity) in females, daily, in the diet. Examination included clinical signs and mortality, body weight and body weight gain, food consumption and compound intake, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology. No treatment related effects were identified on clinical

signs and mortality, food consumption, clinical chemistry, hematology, gross pathology, and neo-plastic histopathology. Body weights and body weight gain were significantly lower in the top dose group throughout the study and in the mid-dose group during the first year of the study. In the eyes, a statistically significantly increased incidence of loss of the outer nuclear layer of the retina was seen in females in the mid and top dose groups. An increased incidence of prominent eosinophilic inclusions was observed in females in the mid and top dose groups (36/50 total and 47/50 total, respectively, vs. 29/50 total controls). ECHA (2021) authors reported that this may have been an exacerbation of an age-related finding. Only the mid-dose was statistically significant. Based on the available data authors established a NOAEL and LOAEL of 102 and 418 mg/kg/day, respectively. This study was assigned a Klimisch score of 1 (reliable without restriction).

- Barber and Topping 1995
  - *Oral:* A GLP compliant 90-day toxicity study (EPA 799.9310) was conducting using male and female Sprague-Dawley rats (20/sex/dose). Rats were administered doses of 0, 54, 277, and 561 mg/kg of DEHT in males, and 0, 61, 309, and 617 mg/kg of DEHT (98.4% purity) in the feed for 90 days. Examination included clinical signs and mortality, body weight and body weight gain, food consumption and compound intake, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology. No effects were reported on clinical signs and mortality, body weight and body weight gain, food consumption and compound intake, ophthalmoscopic examination, clinical chemistry, urinalysis, gross pathology, and histopathology. Mean hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) were significantly lower than controls in the top dose male group (4-5% decreases). Mean MCH values were also lower in the mid-dose male rat group (2%). MCV and MCH values were significantly decreased in mid- and top-dose female rats (3%). Authors concluded that changes in hematology were minimal in severity, and not clearly dose-dependent and were therefore not of biological significance. Absolute liver weight increases (9%) and liver weights relative to body weights ratio increase (11%) were measured in males in the top-dose group. Only relative liver weight changes reached statistical significance. In females, the absolute liver weight was increased by 7% and the relative liver weight was increased by 9% in the top-dose groups. Again, only relative liver weight changes reached statistical significance. Based on the available data, study authors established a NOEL and LOEL of 277 and 561 mg/kg based on hematological and liver weight changes.
- ECHA 2021
  - *Oral:* In a subacute oral toxicity study that predates GLP, male Sprague-Dawley rats (5/dose) received DEHT in the diet at 0, 0.1 or 1.0% for 10 days (equivalent to 0, 85.0 and 885 mg/kg/day, respectively, according to ECHA dossier). Parameters examined were clinical observation, body weight, feed consumption, hematology, clinical chemistry, organ weights (liver and kidney only), and histopathology (multiple tissues). No adverse effects were observed, and the authors identified the NOAEL at 1.0% (885 mg/kg/day). This study was assigned a Klimisch score of 2 (reliable with restrictions).
- Eastman 2010, ECHA 2021
  - *Oral:* In a 21-day dietary study, Fischer 344 rats (5/sex/dose) were given diets containing 0, 0.1, 0.5, 1.0, 1.2, or 2.5% DEHT, which was equivalent to 0, 100, 500, 1,000, 1,250, and 2,000 mg/kg/day according to Eastman. Significant decreases in feed consumption and associated weight gain and terminal body weight were observed at the highest dose. In addition, animals exhibited clinical signs of toxicity (unspecified). Body weight development at other doses was comparable to controls. Although absolute liver weights

were not changed, relative liver weight in males was increased at the highest dose. Significant decrease in absolute kidney weights was measured at 1.0% and 2.5%, with a decrease in relative weight observed at 2.5% only in males. Significant increase in absolute liver weight was only found at 1.2% in females, but relative liver weight was significantly increased at 1.0, 1.2, and 2.5%. Absolute and relative kidney weight was significantly decreased in females at the high dose. The study authors attributed the increased relative organ weights at the highest dose to severe decreases in terminal body weight. At 2.5%, there was a significant decrease in serum triglycerides in males, and an increase in females. Females also had significant increases in cholesterol at the highest dose, but a significant decrease was found at 1.0%. Some evidence of peroxisomal proliferation was observed upon microscopic examination at 2.5%, and corresponding significant increases in hepatic enzyme activities were also observed. Males at 1.2% had a slight but significant increase in the activity of one enzyme (unspecified). The authors indicated that a confounding factor for the observed peroxisomal effects was that feed restriction alone could double the peroxisomal oxidizing activity. The authors identified the NOAEL at 1.2% (1,250 mg/kg/day). This study was assigned a Klimisch score of 1 (reliable without restriction).

- ECHA 2021
    - *Dermal:* In a subacute toxicity study that predates GLP, Dunkin-Hartley guinea pigs (5/dose) were exposed to neat DEHT (purity not specified) on the skin under non-occlusive conditions once per day for a total of 9 applications over 11 days at doses of 813 or 1,144 mg/kg/day. Parameters examined only included clinical observation and body weight. There was no mortality during the study. Moderate erythema was observed in one animal and severe erythema was observed in another animal upon first application. Erythema did not diminish in severity over the course of the study. Slight edema was found in all animals, but was reversible at study termination. All animals gained weight. No NOELs were identified for this study due to limited endpoints examined. The authors concluded that DEHT is not acutely toxic following repeated exposure, but may cause moderate irritation. This study was assigned a Klimisch score of 2 (reliable with restrictions).
    - *Inhalation:* In a subacute toxicity study that predates GLP, male Sprague-Dawley rats (5/dose) were exposed to DEHT (purity not specified) by whole body inhalation at an average concentration of 0 or 0.0718 mg/L for 6 hours/day, 5 days/week for 14 days. Parameters examined included clinical observation, body weight, clinical chemistry, hematology, liver and kidney weight, and histopathology of multiple organs. No treatment-related effects were reported. The study authors identified the NOAEC at 0.0718 mg/L. This study was assigned a Klimisch score of 2 (reliable with restrictions).
- Based on the weight of evidence, a score of Low was assigned. Limited data for the inhalation and dermal routes of exposure are available and are insufficient for GHS classification. High quality subchronic and chronic oral studies identified NOAELs greater than 100 mg/kg/day, which do not warrant GHS classification.

Neurotoxicity (N)

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

DEHT was assigned a score of Low for neurotoxicity (single dose) based on lack of clinical signs of neurotoxicity in acute toxicity studies via the oral, dermal and inhalation routes. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data are available and they are not classified under GHS (CPA 2018b). The confidence in the score is low as no specific evaluation of neurotoxicity was performed in the acute toxicity studies identified.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- As described in single-dose systemic toxicity section above, no clinical signs of toxicity were observed in animals treated with DEHT at doses well above the GHS classification thresholds. In addition, DEHT did not cause transient narcotic effects at any dose levels that would warrant classification to GHS category 3. Therefore, a score of Low was assigned.

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

DEHT was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of adequate data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Deyo 2008, ECHA 2021
  - A GLP-compliant 104-week chronic toxicity/carcinogenicity study using male and female Fischer 344 rats (50/sex/dose) was conducted in accordance with EPA OPPTS 870.4200. Rats were administered DEHT at doses of 0, 79, 324, and 666 mg/kg in males and 0, 102, 418, and 901 mg/kg (> 98% purity) in females daily in the diet. During the treatment phase, animals were inspected twice daily for evidence of ill-health or reaction to treatment. EPA OPPTS 870.4200 recommends weekly examinations of central nervous system effects including tremors and convulsions, autonomic effects including salivation, changes in activity level, gait, and posture, reactivity to handling or sensory stimuli, and bizarre behavior. Study investigators reported that exposure to DEHT had no effect on the behavior of the animals and minimal clinical signs of toxicity were observed. However, the publication available publication or the ECHA record of this study does not specifically describe the observation or evaluation of the neurotoxicity endpoints recommended in EPA OPPTS 870.4200. This study was assigned a Klimisch score of 1 (reliable without restriction).
- Barber and Topping 1995, ECHA 2021
  - A GLP compliant 90-day toxicity study, equivalent or similar to EPA 799.9310, was conducting using male and female Sprague-Dawley rats (20/sex/dose). Rats were administered doses of 0, 54, 277, and 561 mg/kg of DEHT in males, and 0, 61, 309, and 617 mg/kg of DEHT (98.4% purity) in the feed for 90 days. Each rat was removed from its cage on the mornings of days 0, 3, and 7, and weekly thereafter for examination. Every workday afternoon and on the mornings on which examinations were not conducted, cage side observations were conducted including, but was not limited to: examination of the hair, skin, eyes, motor activity, feces, and urine. EPA 799.9310 recommends evaluations of central nervous system effects including tremors and convulsions, autonomic effects including salivation, changes in activity level, gait, and posture, reactivity to handling or sensory stimuli, and bizarre behavior. Study investigators reported that DEHT did not produce major organ or general systemic toxicity. However, the publication available online does not specifically describe the observation or evaluation of the neurotoxicity endpoints recommended in EPA 799.9310.
- Based on the weight of evidence, a score of Data Gap was assigned. Although two repeated dose oral toxicity studies are available, examination of specific neurotoxicity endpoints including evaluations of central nervous system effects including tremors and convulsions, autonomic effects including salivation, changes in activity level, gait, and posture, reactivity to handling or sensory stimuli, and bizarre behavior were not specifically described in the publications or in the ECHA

record. As confirmation of evaluation of neurotoxicity endpoints was not available, a score of Data Gap was assigned.

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

DEHT was assigned a score of Low for skin sensitization based on negative sensitization data in a human repeat patch test and a guinea pig sensitization study. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when negative data are available and the chemical is not GHS classified (CPA 2018b). The confidence in the score is high as the score is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- UNEP 2003
  - A non-GLP compliant dermal sensitization study (footpad method) was conducted using guinea pigs (strain/sex not reported, n=5). Guinea pigs were exposed to a 1% solution of DEHT (purity not reported) via injection into the footpad followed by a 1% dermal application challenge dose. No signs of sensitization were observed and DEHT was reported as non-sensitizing under the tested conditions. This study was reported with a reliability score of 2 (valid with restrictions).
  - A dermal sensitization (modified Draize method) was conducted using human volunteers (9/sex) following good clinical practices. Humans were exposed nine dermal applications of 0.5% DEHT in acetone under semi-occlusive conditions over a three-week induction period. Following a two-week rest period a challenge dose of 0.5% was applied to the skin. DEHT was non-irritating and non-sensitizing in all volunteers. This study was reported with a reliability score of 1 (reliable without restriction).
- ECHA 2021
  - DEHT (purity not reported) was not sensitizing in a human repeated insult patch test (HRIPT) conducted following good clinical practices. DEHT (0.5% in acetone) was applied to the backs of humans (n=203) three times a week for three weeks under semi-occlusive conditions for 24 hours. After the induction phase, participants were allowed a rest period for up to 17 days and then a single dermal challenge using naïve sites was applied. DEHT was non-irritating and non-sensitizing. This study was assigned a Klimisch score of 1 (reliable with restriction).

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

DEHT was assigned a score of Low for respiratory sensitization based on a lack of structural alerts and negative results in dermal sensitization studies, according to ECHA's guidance. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when negative data are available and the chemical is 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
  - *Screening:* Not present on any screening lists
- OECD 2020
  - DEHT does not contain any structural alerts for respiratory sensitization (Appendix F).
- 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 DEHT 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 DEHT, and as DEHT does not contain any structural alerts for respiratory sensitization (OECD 2020), DEHT is not expected to be a respiratory sensitizer.

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

DEHT was assigned a score of Low for skin irritation/corrosivity based on negative results in dermal irritation studies in rabbits tested with the neat substance and humans tested with up to 0.5%. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when negative data are available and the chemical is not GHS classified (CPA 2018b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2021
  - A GLP compliant skin irritation/corrosion study (OECD Guideline 404) was conducted using male and female New Zealand white rabbits (2 male/1 female). Rabbits were exposed to 0.5 mL of undiluted test material (purity 98.21%) under occlusive conditions for 4 hours with a 72-hour observational period following exposure. Average scores of 0.0 were reported for erythema and edema, and DEHT was reported as non-irritating under the tested conditions. This study was assigned a Klimisch score of 1 (reliable without restriction).
- UNEP 2003
  - A non-GLP compliant skin irritation/corrosion study (method not reported) was conducted using Male Duncan-Hartley guinea pigs (n=3). Guinea pigs were exposed to 0, 4,920, 9,840, and 19,680 mg/kg of DEHT (purity not reported) under occlusive conditions for 24 hours. Two weeks after exposure the high dose animal showed moderate edema and slight desquamation and severe edema was reported in the low and mid- dose animals. DEHT was reported as slightly irritating under the tested conditions by the authors. This study was reported with a reliability score of 2 (valid with restrictions). *However, current guidelines only specify a 4-hour exposure time and require at least 3 animals per exposure group. Therefore, the reliability of this study is limited in terms of GHS classification.*
  - A primary dermal irritation study (method not reported) was conducted using human volunteers (9/sex) following good clinical practices. Humans were exposed to 0.01, 0.05, 0.1, 0.2, and 0.5% of the test substance under semi-occlusive conditions for three 24-hour periods. Overall irritation scores ranged from 0.00 to 0.11 and the test substance was reported as non-irritating under the tested conditions. This study was reported with a reliability score of 1 (valid without restriction).

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

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

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2021
  - A GLP compliant eye irritation/corrosion study (OECD Guideline 405) was conducted using male and female New Zealand white rabbits (1 male/2 female). Rabbits were exposed to 0.1 ml neat DEHT (98.21% pure) in one eye for 4 hours with a 72-hour observational period following exposure. No corneal opacity or iritis was observed during the study. Conjunctivitis and redness were reported up to 48 hours after administration and all reported effects were fully reversible within 72 hours. The authors reported that the mean 24, 48, and 72 h scores for conjunctivitis were redness were < 2. Therefore, DEHT is not classifiable as a GHS eye irritant. This study was assigned a Klimisch score of 1 (reliable without restriction).
- UNEP 2003
  - A non-GLP compliant eye irritation/corrosion study (method not reported) was conducted using New Zealand white rabbits (n=6, sex not reported). Rabbits were exposed to 0.1 ml of the test substance (purity not reported) in one eye. At 24 h after exposure, one rabbit showed adnexal staining of the nictitating membrane. At 48 h after exposure all animals appeared normal. This study was reported with a reliability score of 1 (valid without restriction). *Following GHS criteria, DEHT is not classified as an irritant as all effects were reversible within a 48-hour time period.*

Ecotoxicity (Ecotox)

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

DEHT was assigned a score of Low for acute aquatic toxicity based on a lack of effects at the saturation level for DEHT. Although Environment Canada classified DEHT as inherently toxic based on predicted EC_{50} value in daphnia, this assessment did not consider the water solubility of the compound. Therefore, ToxServices did not rely on this screening list to assign a score for this endpoint. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when L/EC_{50} values are they are greater than 100 mg/L or there are no effects at saturation, and they are not classifiable under GHS (CPA 2018b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* EC - CEPA DSL - Inherently Toxic in the Environment
    - Based on predicted EC_{50} of 0.0377 mg/L in daphnia by Topkat v6.1.
- ECHA 2021
  - An LC_{50} value of > 0.25 mg/L was identified in *Oncorhynchus mykiss* (rainbow trout, 7-day) (GLP-compliant, Klimisch score 1 (reliable without restriction)).
- UNEP 2003
  - A LC_{50} value of ≥ 984 mg/L was identified in *Pimephales promelas* (fathead minnow, 96-hr).
  - An EC_{50} value of > 1.4 µg/L was identified in *Daphnia magna* (aquatic invertebrate, 48-hr).
  - An EC_{50} value of > 0.860 mg/L was identified in *Selenastrum capriconutum* (algae, 72-hr).
- DEHT has a reported water solubility of 0.4 µg/L (0.0004 mg/L) (ECHA 2021). Based on the available data, no effects are expected at saturation levels for DEHT. Therefore, DEHT was assigned a Low hazard score for acute aquatic toxicity.

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

DEHT was assigned a score of Low for chronic aquatic toxicity based on a lack of effects at the saturation level for DEHT. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when NOECs are greater than 10 mg/L or there are no effects at saturation (CPA 2018b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* EC - CEPA DSL - Inherently Toxic in the Environment
    - Based on predicted EC_{50} of 0.0377 mg/L in daphnia by Topkat v6.1.
- ECHA 2021
  - A NOEC of ≥ 0.28 mg/L was established in *O. mykiss* (fathead minnow, 60-day) (GLP-compliant, Klimisch score 1 (reliable without restriction)).
  - A NOEC of ≥ 0.76 µg/L was established in *D. magna* (daphnid, 21-day) (GLP-compliant, OECD Guideline 211, Klimisch score 1 (reliable without restriction)).
  - A NOEC of ≥ 0.86 mg/L was established in *S. capriconutum* (green algae, 72-hour) (GLP-compliant, OECD Guideline 201, Klimisch score 1 (reliable without restriction)).
- DEHT has a reported water solubility of 0.4 µg/L (ECHA 2021). Based on the available data, no effects are expected at saturation levels for DEHT. Therefore, DEHT was assigned a Low hazard score for chronic aquatic toxicity.

Environmental Fate (Fate)

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

DEHT was assigned a score of Very Low for persistence based on meeting the readily biodegradable criteria following a GLP-compliant OECD Guideline 301B biodegradation study under modern guidelines. In addition, it is predicted to mainly partition to sediment in the environment. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when they meet the 10-day window in ready biodegradation studies when their predominant compartments are water, soil, or sediment (CPA 2018b). The confidence in the score is high as it is based on high quality data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2021
  - A GLP-compliant biodegradation study (OECD Guideline 301B "Ready Biodegradation: CO_2 Evolution Test") was conducted under aerobic conditions at a concentration of 10 mg/L. DEHT had a total of 73.05% biodegradation within 28 days and met the 10-day biodegradation window. DEHT was reported as readily biodegradable by study authors. This study was assigned a Klimisch score of 1 (reliable without restriction).
- UNEP 2003
  - A (GLP status not reported) 28-day shake flask biodegradation test (similar to OECD Guideline 301B) was conducted under aerobic conditions at a concentration of 1.04 mg/L. DEHT was found to have 40.2% biodegradation after 28 days and was not considered to be readily biodegradable. This study was reported with a reliability score of 1 (valid without restriction).
- U.S. EPA 2017
  - DEHT was predicted to be readily biodegradable by BIOWIN of EPI Suite™. Fugacity modeling (EQC model, as recommended by EPI Suite™ based on the predicted partition coefficient) indicates that 67.8% DEHT will partition to sediment with a half-life of 135

days, 28% will partition to soil with a half-life of 30 days, and 3.75% will partition to water with a half-life of 15 days (Appendix G).

Bioaccumulation (B) Score (vH, H, M, L, or vL): L
DEHT was assigned a score of Low for bioaccumulation based on a measured BCF of 396. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when BCF values are > 100 to 500 (CPA 2018b). The confidence in the score is high as it is based on a well-conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2021
  - DEHT has a measured BCF of 393 in *Crassotrea virginica* following EPA OPPTS 850.1710 (Oyster Bioconcentration Test). Following GreenScreen® criteria, chemicals with a BCF < 500 are considered to have low potential for bioaccumulation. This study was assigned a Klimisch score of 1 (reliable without restriction).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
DEHT was assigned a score of Low for reactivity based on a structure indicating that it is not an organic peroxide, does not contain reactive groups associated with self-reactive or oxidizing substances, is not an organometallic substance that may produce flammable gases on contact with water, and does not contain alerts for explosivity. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when available data indicate that the chemical does not warrant GHS classification for any of the reactivity sub-endpoints (CPA 2018b). The confidence in the score is low due to the lack of experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Eastman 2020
  - DEHT has an HMIS rating of 0 for physical hazard ("materials that are normally stable, even under fire conditions and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of DEHT. These procedures are listed in the GHS (UN 2019).
  - Based on the structure of its components or moieties, DEHT is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix H).
  - Based on the structure of its components or moieties, DEHT is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.

Flammability (F) Score (vH, H, M, or L): L
DEHT was assigned a score of Low for flammability based on a flash point of 212°C, which is above the 93°C cut-off criteria to be classified as a flammable liquid under GHS. GreenScreen® criteria classify chemicals as a Low hazard for flammability when the chemical is not GHS classified as a flammable liquid (CPA 2018b). The confidence in the score is high as it is based on experimental data.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2021
  - DEHT has a flash point of 212°C (ASTM D3278), which is above the 93°C cut-off criteria to be classified as flammable liquid under GHS (UN 2019).

Use of New Approach Methodologies (NAMs)[9] in the Assessment

Table 4: Summary of NAMs Used in the GreenScreen® Assessment		
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* assays for gene mutation and chromosomal aberration
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays, *in vitro* assays for hormonal activity
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™
Bioaccumulation	N	

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

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for DEHT (CAS #6422-86-2)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	DEHT	6422-86-2	L	L	L	*L*	DG	L	L	L	*L*	DG	L	*L*	L	L	L	L	vL	L	*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	No	No	No
3	No	No	No	No			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
DEHT	4

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

Table 6

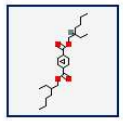
Chemical Name	Final GreenScreen® Benchmark Score
DEHT	3DG

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												
3												
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	3DG

APPENDIX C: Pharos Output for DEHT (CAS #6422-86-2)



6422-86-2

Bis(2-ethylhexyl) terephthalate

ALSO CALLED [144981-82-8] Bis(2-ethylhexyl) terephthalate (primary CASRN is 6422-86-2), [1264916-12-2] Bis(2-eth...

View all synonyms (24)

Share Profile

Hazards | Properties | Functional Uses | Process Chemistry | Resources

All Hazards View

Show List Hazard Summary | Show PubMed Results | Request Assessment | Add to Comparison

		Group I Human					Group II and II* Human								Ecotox			Fate		Physical		Mult	Non-GSLT				
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
GreenScreen Assessment	BM-3dg	L	L	L	L	DG	L	L	L	L	DG	L	L	L	L	L	L	-	vL	L	L	L	-	-	-	-	R

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Acute aquatic toxicity; Chronic aquatic toxicity	U	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)	

Restricted Substance Lists (1)

- CA SCP - Candidate Chemicals: Candidate Chemical List

Positive Lists (1)

- German FEA - Substances Hazardous to Waters: Non-Hazardous to Water (Water Hazard Class 0 NWG)

APPENDIX D: GreenScreen® Criteria for Endocrine Activity

CPA's GreenScreen® guidance (CPA 2018a) defines an endocrine active substance as:

> "a substance having the inherent ability to interact or interfere with one or more components of the endocrine system resulting in a biological effect, but need not necessarily cause adverse effects. Endocrine activity is considered as a collection of modes of action, potentially leading to adverse outcomes, rather than a (eco)toxicological hazard in itself."

The guidance specifies a two-step approach to classifying endocrine activity. First, a preliminary hazard level is assigned, then a final hazard level is assigned using expert judgement and strength of evidence. Rules for assigning a data gap for endocrine activity are clearly stated in Section 8.1.1.4 of the guidance (reprinted below from CPA 2018a):

A2.2.2 Endocrine Activity

A preliminary hazard level or range is assigned by determining whether the chemical is endocrine active. This is done by searching all GreenScreen Specified Lists and available data. For chemicals that are endocrine active, determine whether there is a plausibly related adverse human health effect, and identify the associated level of hazard. Assigning the final hazard level for Endocrine Activity will use expert judgment and a strength of evidence approach.[1]

A2.2.2.1 Low Hazard

1. Low hazard classification requires data for multiple endocrine pathways. Negative data on at least the following five pathways is required to assign a low hazard classification for endocrine activity: androgenicity, anti-androgenicity, thyroid effects, estrogenicity, and anti-estrogenicity.

A2.2.2.2 Moderate Hazard

1. Endocrine Activity is classified as Moderate if there is indication of Endocrine Activity in the scientific literature.
   a. All chemicals with data suggesting Endocrine Activity associated with adverse effects are initially assigned as Moderate. It is also acceptable to assign a range (Moderate or High) to indicate preliminary classification.
   b. For chemicals listed on GreenScreen Specified Lists for Endocrine Activity, other than EU – SVHC Authorisation List, classify them initially as Moderate. It is also acceptable to assign a range (Moderate or High) to indicate preliminary classification.
   c. Chemicals initially classified as Moderate using GreenScreen Specified Lists should be further reviewed using the scientific literature to confirm classification.

A2.2.2.3 High Hazard

1. If the chemical being assessed is present on the EU – SVHC Authorization List for Endocrine Activity, classify it as High hazard for Endocrine Activity.
2. Where Endocrine activity is plausibly[2] related to an adverse effect such as Carcinogenicity, Reproductive Toxicity, Developmental Toxicity and/or Systemic Toxicity (Repeated dose, typically, thyroid) and the hazard endpoint for the plausibly related adverse effect has been classified as High or very High, modify the hazard level for Endocrine Activity from Moderate to High. Where the adverse effect is not plausibly related or the hazard endpoint for the plausibly related adverse effect has been classified as Moderate, do not modify the Endocrine Activity level. See Table A2.2.

TABLE A2.2: **Modified Endocrine Activity Classifications for Select Endpoints**

Endpoint	Initial Endocrine Activity Classification	Plausibly Related Hazard Endpoint Classification	Modified Endocrine Activity Classification
Carcinogenicity	M	H	H
Carcinogenicity	M	M	M
Reproductive Toxicity	M	H	H
Reproductive Toxicity	M	M	M
Developmental Toxicity	M	H	H
Developmental Toxicity	M	M	M
Systemic Toxicity—repeated dose (Thyroid)	M	vH	H
Systemic Toxicity—repeated dose (Thyroid)	M	H	H
Systemic Toxicity—single dose (Thyroid)	M	M	M

A2.2.2.4 Data Gaps

1. A chemical that is not listed on any GreenScreen Specified Lists for Endocrine Activity and for which test data do not exist shall be assigned Data Gap.

2. Data Gaps are assigned using expert judgment: 1) if there is no evidence of Endocrine Activity, but data are incomplete for one or more of the five required endocrine mediated pathway, and/or 2) when a study demonstrating Endocrine Activity is judged to be inadequate.

APPENDIX E: Benchmark Dose Modeling of Reduced Pup Body Weights in the Two-Generation Reproductive Toxicity Study (Farber et al. 2007a)

BMD Modeling Methods

ToxServices performed benchmark dose modeling on the mean pup body weight on PND 1 and PND2 in male and female F1 and F2 offspring separately. The Benchmark Dose Modeling Software (BMDS) version 2.60 and the complementary BMDS Wizard for continuous data were used. ToxServices consulted Dr. Jeff Gift from the U.S. EPA's National Center for Environmental Assessment to identify appropriate approaches to analyze this type of dataset where the dam body weight may affect the pup body weight. Dr. Gift advised ToxServices to use two approaches (Gift 2015):

- To model the litter means as individual (dam) responses (i.e. n = the number of litters per dose)
- To ignore litter variability and assess variability across pups at each dose (i.e. n = the total number of pups per dose)

ToxServices used both approaches to model data, but the second approach did not result in any viable model fit for any of the datasets (data not shown). Therefore, ToxServices only analyzed output from the first approach. The benchmark response (BMR) of 5% relative deviation (i.e., a 5% decrease of body weight from control) was used as a conservative approach for threshold evaluation, although the default BMR is 1 standard deviation (SD, ~10% change from the control) or 10% relative deviation (less conservative). As shown in Table 1, none of the continuous models in BMDS version 2.60 appropriately fit the data of F1 male pup weight on PND 1 or F1 female pup body weight on PND 1 and 21. In addition, the BMD and BMDL values are lower for PND21 data compared to PND1 data, indicating that the decrease in body weight is more significant on PND21 than on PND1.

Results

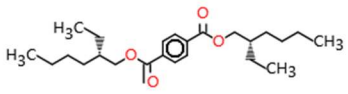
As shown in the Table E-1 below, all of the BMD_{05} values for modeled pup weight at either PND1 or 21 are greater than the Safer Choice cutoff of 250 mg/kg/day for reproductive and developmental toxicity. The 95% lower confidence bound of BMD_{05} (i.e., $BMDL_{05}$) ranges from 197 to 546 mg/kg/day.

Table E-1: Summary of Benchmark Dose Modeling on Farber et al. (2007) Study for DEHT

Pup Weight Modeled	BMD_{05} (mg/kg/day)	$BMDL_{05}$ (mg/kg/day)	Best Fitting Model	Notes[1]
F1 Male PND1	NA	NA	NA	No models fit
F1 Male PND21	284	197	Polynomial 3	
F1 Female PND1	NA	NA	NA	No models fit
F1 Female PND21	NA	NA	NA	No models fit
F2 Male PND1	1021	521	Power and Linear	Both models fit equally well
F2 Male PND21	329	211	Polynomial 3	
F2 Female PND1	1102	546	Linear	
F2 Female PND21	341	224	Polynomial 3	

[1]The best fit models were determined by default criteria built-in in the BMDS Wizard.

APPENDIX F: OECD Toolbox Respiratory Sensitization Modeling Results for DEHT (CAS #6422-86-2)

Filter endpoint tree...	1 [target]
Structure	
⊞ **Structure info**	
⊞ **Parameters**	
⊞ **Physical Chemical Properties**	
⊞ **Environmental Fate and Transport**	
⊞ **Ecotoxicological Information**	
⊞ **Human Health Hazards**	
⊟ **Profiling**	
⊟ **Endpoint Specific**	
Respiratory sensitisation	No alert found

APPENDIX G: EPISuite Modeling Results for DEHT (CAS #6422-86-2)

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

CAS Number: 6422-86-2
SMILES : O=C(OCC(CCCC)CC)c(ccc(c1)C(=O)OCC(CCCC)CC)c1
CHEM : 1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester
MOL FOR: C24 H38 O4
MOL WT : 390.57
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 8.39
Boiling Point (deg C) : 375.00
Melting Point (deg C) : -48.00
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): 0.0004
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 8.39

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 416.95 (Adapted Stein & Brown method)
Melting Pt (deg C): 63.87 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 3.34E-005 (Modified Grain method)
VP (Pa, 25 deg C) : 0.00445 (Modified Grain method)
MP (exp database): -48 deg C
BP (exp database): 400 deg C
VP (exp database): 2.50E-06 mm Hg (3.33E-004 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 0.001009
log Kow used: 8.39 (user entered)
melt pt used: -48.00 deg C
Water Sol (Exper. database match) = 0.0004 mg/L (23 deg C)
Exper. Ref: EASTMAN KODAK

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 0.0012776 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.18E-005 atm-m3/mole (1.20E+000 Pa-m3/mole)
Group Method: 1.02E-005 atm-m3/mole (1.03E+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: 4.291E-002 atm-m3/mole (4.348E+003 Pa-m3/mole)
VP: 3.34E-005 mm Hg (source: MPBPVP)
WS: 0.0004 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 8.39 (user entered)
Log Kaw used: -3.317 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 11.707
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.1268
Biowin2 (Non-Linear Model) : 0.9999
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.2132 (weeks)
Biowin4 (Primary Survey Model) : 4.2803 (hours-days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.6891
Biowin6 (MITI Non-Linear Model): 0.7107
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.2275
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): 0.000333 Pa (2.5E-006 mm Hg)
Log Koa (Koawin est): 11.707
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.009
Octanol/air (Koa) model: 0.125
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.245
Mackay model : 0.419
Octanol/air (Koa) model: 0.909

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 21.9554 E-12 cm3/molecule-sec
Half-Life = 0.487 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 5.846 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.332 (Junge-Pankow, Mackay avg)
0.909 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1.172E+005 L/kg (MCI method)
Log Koc: 5.069 (MCI method)
Koc : 2.721E+005 L/kg (Kow method)
Log Koc: 5.435 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 1.563E-001 L/mol-sec
Kb Half-Life at pH 8: 51.338 days
Kb Half-Life at pH 7: 1.406 years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 2.846 (BCF = 702.1 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.0648 days (HL = 1.161 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.004 (BCF = 10.09)
Log BAF Arnot-Gobas method (upper trophic) = 1.516 (BAF = 32.79)
log Kow used: 8.39 (user entered)

Volatilization from Water:
Henry LC: 1.02E-005 atm-m3/mole (estimated by Group SAR Method)
Half-Life from Model River: 115.5 hours (4.811 days)
Half-Life from Model Lake : 1425 hours (59.38 days)

Removal In Wastewater Treatment:
Total removal: 94.03 percent
Total biodegradation: 0.78 percent
Total sludge adsorption: 93.25 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	0.95	11.7	1000
Water	22.6	360	1000
Soil	70.6	720	1000
Sediment	5.83	3.24e+003	0

Persistence Time: 497 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.95	11.7	1000

Water	22.6	360	1000
water	(1.68)		
biota	(20.6)		
suspended sediment	(0.295)		
Soil	70.6	720	1000
Sediment	5.83	3.24e+003	0

Persistence Time: 497 hr

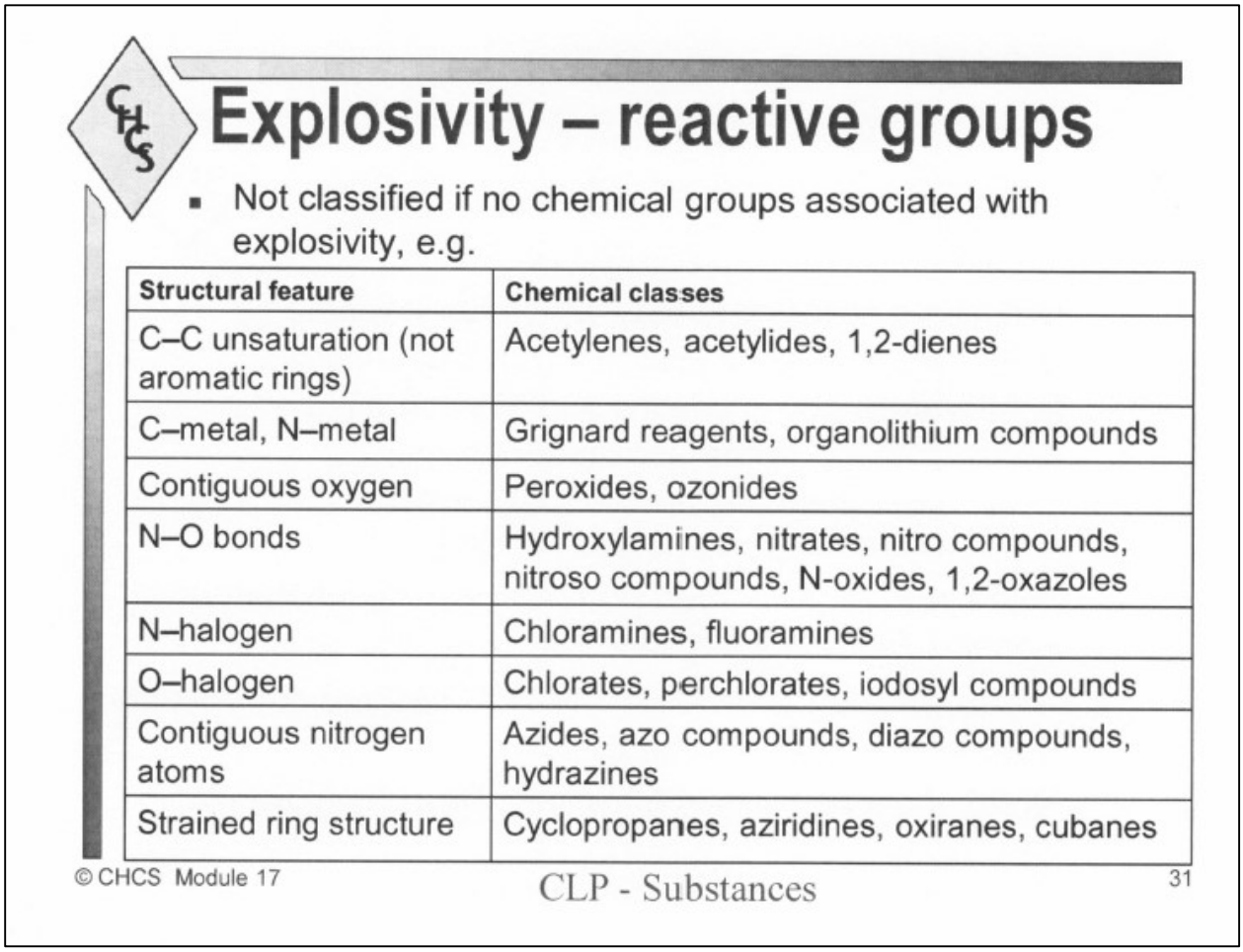
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	**Half-Life (hr)**	**Emissions (kg/hr)**
Air	**0.376**	**11.7**	**1000**
Water	**3.75**	**360**	**1000**
water	**(0.0228)**		
biota	**(0.28)**		
suspended sediment	**(3.45)**		
Soil	**28**	**720**	**1000**
Sediment	**67.8**	**3.24e+003**	**0**

Persistence Time: 1.25e+003 hr

APPENDIX H: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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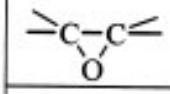
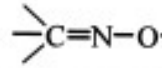
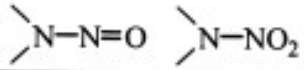
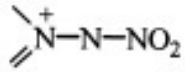
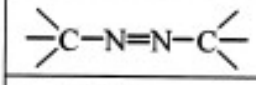
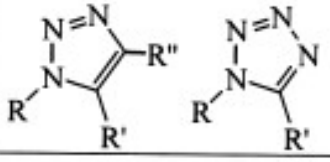
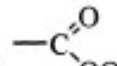
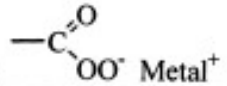
Explosivity – Full List

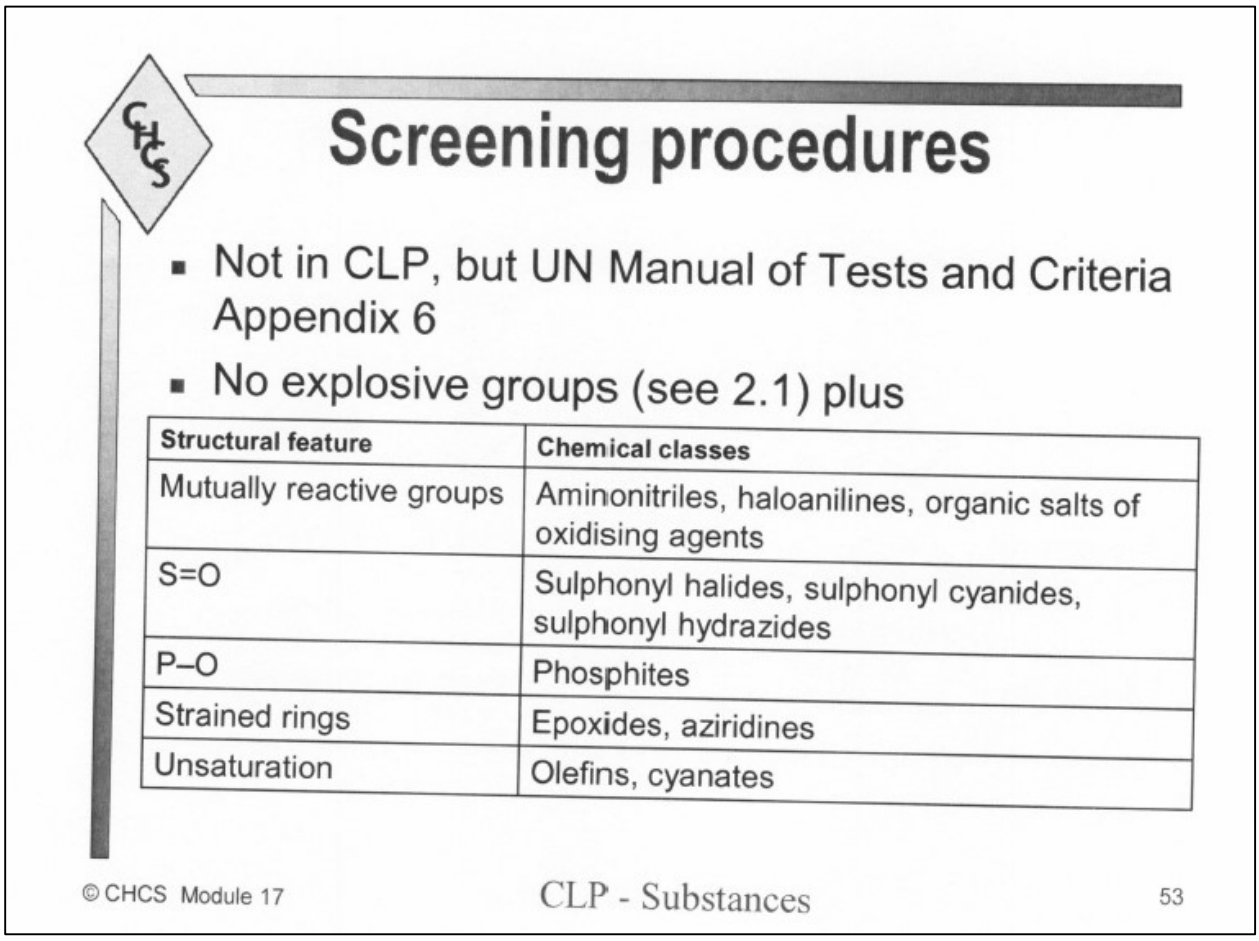
Table R.7.1-28 Chemical groups associated with explosive properties

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

Chemical group	Chemical Class
[1] ROOR',  [2]	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal,  [2]	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. NCl_3, $RNCl_2$	N-Halogen Compounds

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

Self-Reactive Substances



Licensed GreenScreen® Profilers

DEHT GreenScreen® Evaluation Prepared and/or Updated by:

SIGNATURE BLOCK

Chris Schlosser, M.F.S.
Associate Toxicologist
ToxServices LLC

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Toxicologist
ToxServices LLC

SIGNATURE BLOCK

Lindsey Lund, M.S.
Associate Toxicologist
ToxServices LLC

SIGNATURE BLOCK

Jennifer Rutkiewicz, Ph.D.
Senior Toxicologist
ToxServices LLC

SIGNATURE BLOCK

Megan B. Boylan, M.S.
Toxicologist
ToxServices LLC

SIGNATURE BLOCK

Sara M. Ciotti, Ph.D.
Toxicologist
ToxServices LLC

DEHT GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC

SIGNATURE BLOCK

Jennifer Rutkiewicz, Ph.D.
Toxicologist
ToxServices LLC

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC