GreenScreen™ Assessment for 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester (DPHP) (CAS #53306-54-0)

GreenScreen™ Version 1.2 Draft Assessment
Note: Validation Has Not Been Performed on this Green Screen Assessment

Chemical Name: 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester (DPHP) (CAS #53306-54-0)

GreenScreen™ Assessment Prepared By:
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Date: December 19, 2011
Revised: February 10, 2012
Revised: May 9, 2012

GreenScreen™ Assessment QC'd By:
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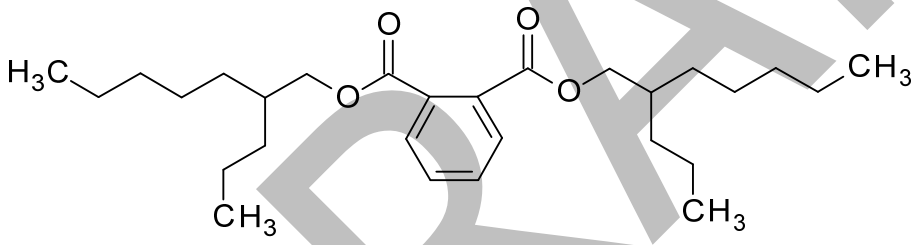
Date: February 13, 2012; May 30, 2012

Confirm application of the *de minimus* rule[1]: Yes

Chemical Name (CAS #):1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester (DPHP) (CAS #53306-54-0)

Also Called: Bis(2-propylheptyl) phthalate

Chemical Structure(s):



Identify Applications/Functional Uses:
(e.g. Cleaning product, TV casing)
1. Plasticizer

Green Screen Rating[2]:
DPHP was assigned a GreenScreen™ Benchmark Score of U (unspecified) based on Data gaps (dg) for Carcinogenicity (C), Neurotoxicity (N) (not listed, but not tested), and Respiratory Sensitization (SnR). As outlined in CPA (2011c) Section III(1)(Benchmarking Chemicals With Data Gaps), permissible data gaps for Group I Human Health endpoints may only include Endocrine Activity and either Reproductive (R) or Developmental (D) Toxicity. In a worst-case scenario, if DPHP were assigned a High score for C, it would be assigned a GreenScreen™ Benchmark Score of 1.

[1] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm.

[2] 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.

GreenScreen™ Hazard Ratings: 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester (DPHP) (CAS #53306-54-0)																			
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*										
dg	L	L	L	*M*	L	dg	L	dg	dg	L	dg	L	L	L	*L*	L	vL	L	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values and lower confidence. Hazard levels in **BOLD** font reflect values based on test data (See Guidance).
Note: Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings[3]:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[4]

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	On CPA Red List[5]?	Green Screen Rating[6]
n/a	**End**	Combustion	Carbon Monoxide	**630-08-0**	**Y**	**1**
n/a	**End**	Combustion	Carbon Dioxide	**124-38-9**	**N**	**N/A**

Introduction

DPHP is a plasticizer used for PVC and vinyl chloride co-polymers. The product is used in automobile undercoating, building materials, wires, cables, shoes, carpet backing, pool liners, and gloves. Concentration of chemical in final products typically ranges from 30-60% (NICNAS 2003).

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M or L): dg
DPHP was assigned a score of data gap for carcinogenicity based insufficient data available to assign a hazard ranking for DPHP or structurally related phthalates.

- Not listed as a known carcinogen by IARC, NTP, U.S. EPA, or CA Prop 65.
- UNEP 2004 –
  - DPHP was evaluated as a part of the High Molecular Weight Phthalate Esters (HMWPE) category. No HMWPE have been evaluated for carcinogenic properties in chronic toxicity or bioassay studies. However, a wide range of lower MW phthalates suggest that high doses may produce liver changes in rodents, but are not relevant to humans. Three chronic toxicity studies have been conducted on diisononyl phthalate (DINP). In rat studies, increases in both liver and kidney tumors were observed. These changes were primarily related to the induction of peroxisome proliferation and tumors in both kidneys and liver were considered to be rat specific as a result.

[3] Products that contain phthalates or phthalate alternatives are often plastics. Plastics are often disposed of via incineration. Therefore, health and environmental effects associated with combustion byproducts are of particular concern.
[4] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.
[5] The CPA "Red List" refers to chemicals: 1) flagged as Benchmark 1 using the GreenScreen™ List Translator , or 2) flagged as Benchmark 1 or 2 using the GreenScreen™ List Translator and further assessed and assigned as Benchmark 1. The most recent version of the GreenScreen™ List Translator should be used (CPA 2011b).
[6] GreenScreen reviews of transformation products depend on the GreenScreen Benchmark Score of the parent chemical (See Guidance in CPA 2011c).

- While tumors identified for DINP have been categorized as irrelevant or of unknown relevance to humans, there is still debate as to its overall relevance to humans. Given that DPHP has not been tested, and the data for structurally similar phthalates is still in question, this endpoint is assigned a data gap score for insufficient data available.

Mutagenicity/Genotoxicity (M) Score (H, M or L): L
DPHP was assigned a score of low for mutagenicity based on negative mutagenicity data in an Ames assay and negative mutagenicity and clastogenicity data for structurally similar analogs in an UNEP SIDS assessment.

- REACH 2010 –
  - A GLP-compliant bacterial reverse mutation assay (OECD 471) was conducted utilizing *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation at concentrations of 0, 20, 100, 500, 2,500 and 5,000 µg/plate (purity not reported). DPHP was found to be negative for mutagenicity under all tested conditions (BASF 1995). Furthermore, the REACH authors concluded that negative genotoxicity studies *in vitro* and *in vivo* for structurally similar phthalates further support that DPHP is not a genotoxic compound.
- UNEP 2004 –
  - All tested HMWPE category members were negative for mutagenicity following Ames assays. In addition, a number of tested chemical were negative for genotoxicity following mouse lymphoma tests. Additional testing of a C13 phthalate ester showed that it did not induce structural chromosomal aberrations or polyploidy in Chinese Hamster Liver cells at up to 4.75 mg/ml (JMHW Undated).

Reproductive Toxicity (R) Score (H, M, or L): L
DPHP was assigned a score of low for reproductive toxicity based on no effects observed in reproductive two-generation toxicity study.

- REACH 2010 –
  - A GLP-compliant 2 generation reproductive toxicity study (OECD Test Guideline 416) was conducted using male and female Wistar rats (25/sex/group). Rats were administered doses of 0, 40, 200 and 600 mg/kg (purity not reported) in the diet over the two parental generations (F0 and F1). No effects were reported on fertility or reproductive performance in any group. In addition, viability, sex ratio, and sexual developmental were not affected at any point in the study in any group. Study authors reported a NOAEL of 600 mg/kg for the study (BASF 2009a).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L): L
DPHP was assigned a score of low for developmental toxicity based on a LOAEL of 1,000 mg/kg assigned from a developmental toxicity study and not being classified as a reproductive toxicant following GHS criteria.

- REACH 2010 –
  - A GLP-compliant developmental toxicity study (OECD Test Guideline 414) was conducted using female Wistar rats (25/group). Rats were administered doses of 0, 40, 200 and 1,000 mg/kg (purity not reported) of the test substance on days 6 through 19 of gestation. In the high dose group significant changes were observed on gravid uterus weight, resorptions, post implantation loss value, and a borderline effect of fetal morphology. Study authors reported a NOAEL and LOAEL of 200 and 1,000 mg/kg based on the reported effects (BASF 2003).
  - A second GLP-compliant unpublished study was reported following the same guidelines and dose levels. No effects were observed on developmental toxicity and a NOAEL of 1,000 mg/kg was reported (BASF 1995b).
  - DPHP was not classified as a reproductive/developmental by REACH authors based on EU or GHS criteria.

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

- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).

DPHP was assigned a score of Moderate for endocrine activity based on full review of 90-day, reproductive, and developmental toxicity studies disclosed under a Non-Disclosure Agreement with BASF. For ToxServices discussion of this evaluation, please refer to Appendix C.

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

Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

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

DPHP was assigned a score of Low for acute mammalian toxicity based on oral and dermal LD_{50} values above 2,000 mg/kg and an inhalation LC_{50} greater than 5.0 mg/L.

- REACH 2010 –
  - *Oral* LD_{50} (Wistar rat) >5,000 mg/kg (GLP-Compliant, OECD Test Guideline 401) (Biosearch Inc 1982a).
  - *Dermal* LD_{50} (rabbit) > 2,000 mg/kg (GLP-Compliant, OECD Test Guideline 402) (Biosearch Inc 1982b).
  - *Inhalation* LC_{50} (Wistar rat) > 20.5 mg/L (GLP-Compliant, OECD Test Guideline 403) (Biosearch Inc 1982c).

Systemic Toxicity/Organ Effects incl. immunotoxicity (ST) Score (vH, H, M or L): L

DPHP was assigned a score of Low for systemic toxicity/organ effects based on not being classified by REACH as a GHS toxicant and a LOAEL of 195 mg/kg.

- REACH 2010 –
  - A GLP-compliant 90-day toxicity study (OECD Test Guideline 408) was conducted using male and female Wistar rats (10/sex/group). Rats were administered doses of 0, 39, 195 and 1,170 mg/kg (purity not reported) of DPHP daily for 90-days. At all doses no deaths occurred and no significant effects on body weights and food consumption were reported. Clinical findings including hematology and urinalysis showed an increase in alkaline phosphatase, cyanide-insensitive palmitoyl-CoA-oxidation albumin, and urinary volumes in both sexes in the high dose groups. Also in the high dose groups decreases in hematocrit and triglycerides in males and glucose in females were observed. In male and female rats liver weights were increased in the mid- and high-dose groups, and liver cell hypertrophy was reported in the mid- and high dose group of both sexes. Based on liver changes, a NOAEL and LOAEL of 39 and 195 mg/kg were reported. The study authors reported that based on available data liver effects may have been the result of peroxisome proliferation. The relevance of these effects to humans is not known (BASF 1995c).
  - A second GLP-compliant 90-day toxicity study (method not reported) was conducted using male and female Sprague-Dawley rats (12/sex/group). Rats were administered doses of 0, 40, 420 and 1,000 mg/kg (purity not reported) daily for 90 days. Decreased weight gain and food consumption were reported in mid dose male and high dose males and females. Histology revealed lesions in the zona glomerulosa of the adrenal glands (minimal in mid dose, and moderate at high dose). Increases in liver weights and increases in peroxisome enzyme levels were reported in all treatment groups. However, peroxisome proliferation was only noted in the mid and high-dose groups. Based on available data, a NOAEL and LOAEL of 40 and 420 mg/kg were reported by study authors (CTL 1997).
  - REACH authors reported that no classification under the EU or GHS were required based on available NOAEL and LOAEL values.

Neurotoxicity (N)

Group II Score (single dose: vH, H, M or L): dg

DPHP has been assigned a data gap for neurotoxicity. Although it is not a known neurotoxicant, neurotoxicity testing has not performed on the chemical.

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).

- Not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2011b).
- No relevant data were identified for DPHP.

Group II* Score (repeated dose: H, M, L): dg
DPHP has been assigned a data gap for neurotoxicity. Although it is not a known neurotoxicant, neurotoxicity testing has not performed on the chemical.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2011b).
- No relevant data were identified for DPHP.

Skin Sensitization (SnS) Group II* Score (H, M or L): L
DPHP was assigned a score of low for skin sensitization based on negative results in a guinea pig sensitization study and negative results from sensitization studies of structurally similar phthalates.
- REACH 2010 –
    - DPHP was found to be non-sensitizing to guinea pigs following a modified Buehler test. No further details were provided for this study (Biosearch Inc. 1982d). The Reach authors concluded that results were supported based on data from the skin irritation study reported below and QSAR modeling.
- UNEP 2004 –
    - HMWPE are not skin sensitizers following Maximization tests or Buehler Methods. No further details were provided.

Respiratory Sensitization (SnR) Group II* Score (H, M or L): dg
- No relevant data were identified.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L): L
DPHP was assigned a score of low for skin irritation/corrosivity based on results from an OECD study indicating DPHP is non-irritating and data on structurally similar phthalates that indicate the category is non-irritating.
- REACH 2010 –
    - A GLP-compliant skin irritation study (OECD Test Guideline 404) using male and female New Zealand rabbits (1 male, 2 female). 0.5 ml (purity not reported) of the test substance was applied to the rear flanks of all animals for 4 hours. The skin sites were evaluated 1, 24, 48 and 72 hours following patch removal. Slight erythema was observed in one animal at one hour, and no skin reactions were observed at 48-hours. DPHP was reported to be non-irritating by the study authors.
    - In second study, DPHP was applied to the backs of 6 albino rabbits and no signs of irritation were observed at 72-hours. Study authors reported DPHP as negative for irritation. No further details were provided (BASF 2002a).
- UNEP 2004 –
    - HMWPE are not irritating to the skin or eyes.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L): L
DPHP was assigned a score of low for eye irritation/corrosivity based on results from an OECD study indicating DPHP is non-irritating and data on structurally similar phthalates that indicate the category is non-irritating.
- REACH 2010 –
    - A GLP-compliant acute eye irritation/corrosion study (OECD Test Guideline 405) was conducted using male and female New Zealand rabbits (1 male, 2 female). 0.1 ml (purity not reported) of DPHP was administered into the eye of all three rabbits for a 24-hour period. Rabbits were then observed for 72hr. Slight to moderate conjunctival redness and slight discharge were observed within the initial 24 hour period. All effects were reversible within 48 hours. Based on the available data, the study authors concluded that DPHP was not irritating to the eyes of rabbits (BASF 2002b).
    - A second GLP-compliant acute eye irritation study (method: other) was conducted using male and female (strain not reported) rabbits (3/sex). 0.1g (purity not reported) of DPHP was applied to one of each rabbit for 24 hours and rabbits were observed for 7 days. No tissues observed showed any

effects after 1, 24, 48, or 72 hours. DPHP was reported non-irritating to the eyes (Biosearch Inc 1982e).

- UNEP 2004 –
  - HMWPE are not irritating to the skin or eyes.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M or L): L
DPHP was assigned a score of low for acute aquatic toxicity based on reported L/EC_{50} values of greater than 100 mg/L for daphnia and blue green algae.

- NICNAS 2003 –
  - DPHP has reported L/EC_{50} values of > 100 mg/L (*Daphnia magna*, 48-hr) and > 100 mg/L (*Scenedesmus subspicatus*, 72-hr) (BASF 1995d; 1997).
- UNEP 2004 –
  - HMWPE are not expected to be acutely or chronically toxic to aquatic organisms based on low water solubility.

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): *L*
DPHP was assigned a score of Low for chronic aquatic toxicity based on being rapidly biodegradable and having a low potential for bioaccumulation.

- DPHP is not classifiable for chronic toxicity following GHS criteria as it is expected to be rapidly biodegradable and not expected to bioaccumulate in aquatic species (UN 2011).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): L
DPHP was assigned a score of low for persistence based on meeting inherent biodegradation requirements of the in an OECD persistence study.

- NICNAS 2003 –
  - DPHP has a reported biodegradation of 75% in 28 days following a GLP-compliant OECD Test Guideline 301 "CO_2 Evolution Test" (BASF 2002c).

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
DPHP was assigned a score of vL for bioaccumulation based on a predicted BCF less than 100.

- U.S. EPA 2011-
  - BCFBAF predicts a bioaccumulation factor of 13.27 and a log Kow of 10.36 indicating that this chemical is not likely to be bioaccumulative (please see Appendix B).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M or L): L
DPHP was assigned a score of low for reactivity based on DPHP being reported as not explosive.

- NICNAS 2003 –
  - DPHP is not explosive.

Flammability (F) Score (vH, H, M or L): L
DPHP was assigned a score of low for flammability based on DPHP being reported as not explosive.

- NICNAS 2003 –
  - DPHP is not combustive and has a flash point of > 200°C. GHS categorizes flammable liquids as having a flashpoint of ≤ 93°C (United Nations 2011).

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APPENDIX A: Hazard Benchmark Acronyms (in Alphabetical Order)

AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(Cr) Corrosion/ Irritation (Skin/Eye)

(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
Modeling Results

EPISuite Results

CAS Number: 53306-54-0
SMILES : O=C(OCC(CCCCC)CCC)c(c(ccc1)C(=O)OCC(CCCCC)CCC)c1
CHEM : 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester
MOL FOR: C28 H46 O4
MOL WT : 446.68
---------- EPI SUMMARY (v4.00) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.68 estimate) = 10.36

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 463.36 (Adapted Stein & Brown method)
Melting Pt (deg C): 105.95 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 3.69E-008 (Modified Grain method)
VP (Pa, 25 deg C) : 4.91E-006 (Modified Grain method)
Subcooled liquid VP: 2.29E-007 mm Hg (25 deg C, Mod-Grain method)
: 3.05E-005 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 2.239e-006
log Kow used: 10.36 (estimated)
no-melting pt equation used

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

ECOSAR Class Program (ECOSAR v1.00):
Class(es) found: Esters

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 3.67E-005 atm-m3/mole (3.72E+000 Pa-m3/mole)
Group Method: 4.06E-005 atm-m3/mole (4.11E+000 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 9.686E-003 atm-m3/mole (9.815E+002 Pa-m3/mole)
VP: 3.69E-008 mm Hg (source: MPBPVP)
WS: 2.24E-006 mg/L (source: WSKOWWIN)

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

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.1001
Biowin2 (Non-Linear Model) : 0.9998
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.0892 (weeks)
Biowin4 (Primary Survey Model) : 4.1994 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.6957
Biowin6 (MITI Non-Linear Model): 0.7098
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.1235
Ready Biodegradability Prediction: YES

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

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

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

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1.319E+006 L/kg (MCI method)
Log Koc: 6.120 (MCI method)
Koc : 3.345E+006 L/kg (Kow method)
Log Koc: 6.524 (Kow method)

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

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

log Kow used: 10.36 (estimated)

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

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

Removal In Wastewater Treatment (recommended maximum 95%):
Total removal: 99.99 percent
Total biodegradation: 78.15 percent
Total sludge adsorption: 21.84 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

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

Persistence Time: 538 hr

Appendix C
ToxServices Evaluation of Potential Endocrine Activity

ToxServices agrees that for any phthalate ester, evaluating anti-androgenic effects has become a key focus. ToxServices therefore appreciated the opportunity to review the full reports for reproductive and developmental toxicity studies conducted with DPHP and Hexamoll DINCH. In reviewing these reports, we focused particularly on the following aspects:

- Specific endpoints evaluated: phthalate esters are known to affect certain endpoints, including, for example, AGD, sperm parameters, male sexual maturation (e.g., testes descent and preputial separation), and male reproductive organ weights.
- Evidence of GLP compliance, such as a quality assurance statement and record of audits.
- Presentation of data: mean, standard deviation/error, and statistical analysis of critical endpoints (such as those listed above). Inclusion of historical control data, when appropriate.
- Discussion of results, specifically the degree of agreement between the text and the actual data tables and the degree to which the actual data support characterization of an effect as related or not related to test article administration.

Of particular importance in determining the possible presence of endocrine activity were the two-generation reproductive and developmental studies. As asserted by EPA and EDSTAC, this is the most robust means by which to evaluate effects on estrogen or androgen-related endpoints. In our review of the two-generation study DPHP study, we were able to confirm that appropriate endpoints were evaluated. However, we disagree with the conclusion that there were no effects on these endpoints. Statistically significant changes in some important endpoints were noted, and justification for their lack of relevance was not provided in the report. Given that certain of these endpoints are known to be affected by phthalates, it is reasonable to conclude that changes therein are relevant. We were unable to use Dr. Gray's genomic phthalate screen data to substantiate the conclusion that DPHP is not endocrine active. That DPHP induced no changes in the specific genes included in the assay could indicate a number of things: the DPHP dose level was insufficient to induce such changes; the time course of genomic changes induced by DPHP is different from the time points at which samples were collected for evaluation; DPHP could affect other genes not included in this screen; DPHP could act by an epigenetic mechanism; and, of course, DPHP could do none of these things. However, the in vivo data suggest that DPHP does have an endocrine active effect. In the 90-day study with DPHP, the following findings were noted:

1. Increased basophilic cells in the anterior pituitary;
2. Increased hypertrophy of the follicular epithelium in the thyroid;
3. Hepatocellular hypertrophy; and
4. Induction of enzymes associated with peroxisome proliferation.

Similar findings in the thyroid were noted in the 90-day study with Hexamoll DINCH. To follow up on the thyroid findings with DPHP and Hexamoll DINCH, animals were treated with:

1. Hexamoll DINCH
2. Propylthiouracil
3. Phenobarbital

The mechanism/mode of action for thyroid effects for both phenobarbital and propylthiouracil have been well-characterized and are summarized below.

Propylthiouracil: This chemical acts directly on the thyroid by inhibiting iodine uptake. Without iodine, thyroid hormone diminishes, again resulting in compensatory upregulation of TSH and the subsequent mitogenic effect on the thyroid.

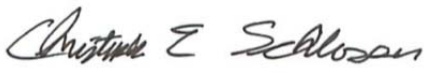
Phenobarbital: induces xenobiotic metabolizing enzymes in the liver, including cytochrome P450 isozymes (e.g., CYP2B) and Phase II conjugating enzymes (e.g., uridine diphosphate-glucuronosyl transferase, or UGT), which are localized to the endoplasmic reticulum in the cell. Phenobarbital-mediated induction of UGT results in increased excretion of thyroid hormone in the rat, thereby activating homeostatic compensatory mechanisms. This results in increased secretion of thyroid stimulating hormone from the pituitary. This has a mitogenic effect on the cells of the

thyroid that ultimately results in a neoplastic effect in rodents. This is an example of how an effect in the liver results in an effect on a distal organ. Induction of thyroid tumors in rats by this particular mechanism is of questionable human relevance due to differences in thyroid hormone turnover and homeostasis between rats and humans (cf. Casarett and Doull's; EPA's thyroid guidance).

The state of the available data does not support the conclusion that thyroid effects are due to peroxisome proliferation. Rather, as explained for phenobarbital, thyroid effects can occur due to proliferation of the endoplasmic reticulum (i.e., microsomes) and induction of xenobiotic metabolizing enzymes therein. The specific enzymes in the liver that underlie the phenobarbital-mediated alterations in thyroid hormone status, the shifts in homeostasis, and the consequent microscopic changes in the thyroid are microsomal, not peroxisomal. Peroxisomes contain enzymes that are responsible for fatty acid oxidation and neutralization of oxidative species such as hydrogen peroxide. Although they are indeed cytochrome P450 isozymes, they are not the enzymes responsible for xenobiotic metabolism in general or thyroid hormone metabolism specifically. Although DPHP and Hexamoll DINCH may indeed affect peroxisomal enzymes, there is no established relationship between these types of enzymes and alterations in thyroid hormone status. Increased peroxisomal enzymes (due to organelle proliferation) would not affect thyroid hormone, based on the current state of knowledge about how thyroid hormone is metabolized. If there is a relationship between the liver effects and the thyroid effects of DPHP and Hexamoll DINCH, it may be due to induction of thyroid hormone metabolism, as in the case of phenobarbital. It is equally possible that DPHP, Hexamoll DINCH, and related materials directly affect the thyroid. The available data (consisting of organ weight and histopathology) cannot differentiate between a direct or indirect effect of DPHP and Hexamoll DINCH on the thyroid. It is highly unlikely that the effect is due to peroxisome proliferation.
For these reasons, ToxServices does not agree with the conclusion that the effects seen in the thyroid are secondary to a peroxisome proliferation effect in the liver. Rather, the two findings co-occur but develop through different mechanisms.

The availability of study reports for DPHP considerably reduces ToxServices concern over data gaps. However, concern remains due to what appears to be unjustified dismissal of potentially relevant effects in reproductive/developmental and thyroid endpoints. The data for DPHP suggests that endocrine activity is occurring; thus, a GreenScreen classification of Moderate is warranted.

1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester (DPHP) Green Screen Evaluation Prepared By:



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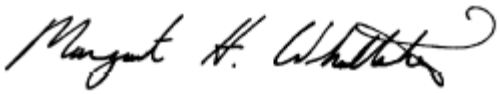
1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester (DPHP) Green Screen Evaluation QC'd By:



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