CPSC Staff Statement on University of Cincinnati Report "Toxicity Review for Di(2-propylheptyl) Phthalate (DPHP)"[1]

June 2019

The U.S. Consumer Product Safety Commission (CPSC) contracted with the University of Cincinnati to conduct a toxicology assessment for di(2-propylheptyl) phthalate (DPHP). The report will be used to inform staff's assessment of products that may contain this compound and is the first step in the risk assessment process.

CPSC staff assesses a product's potential health effects to consumers under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered a "hazardous substance" under the FHSA, a consumer product must satisfy a two-part definition. First, it must be "toxic" under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards of products under the FHSA.

The first step in the risk assessment process is hazard identification, which consists of a review of the available toxicity data for the chemical. If it is concluded that a substance may be "toxic," then CPSC staff will pursue a quantitative assessment of exposure and risk to evaluate whether a specified product may be considered a "hazardous substance."

The toxicity review for DPHP follows. Based on the research conducted by the University of Cincinnati, DPHP does not fit the designation of acutely toxic under the FHSA following single oral exposures and that, due to limited inhalation data, it is unclear whether DPHP fits the designation of acutely toxic under the FHSA via the inhalation route.

[1] This statement was prepared by the CPSC staff, and the attached report was produced by the University of Cincinnati for CPSC staff. The statement and report have not been reviewed or approved by, and do not necessarily represent the views of, the Commission.

TOXICITY REVIEW FOR

Di(2-propylheptyl) Phthalate (DPHP)

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1 Introduction

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with di(2-propylheptyl) phthalate (DPHP).

Literature searches for physico-chemical, toxicological, exposure, and risk information were performed in July 2018 using the CAS number and synonyms (see Appendix 1 for the full list of search terms), and using the following databases:

- EPA SRS
- PUBMED
- RTECS
- TSCATS (included in TOXLINE)
- TOXNET databases, including
    - TOXLINE
    - CCRIS
    - DART/ETIC
    - GENE-TOX
    - HSDB

Searches were conducted for studies indexed to PubMed and Toxline databases from 2007 to the present, because the current report supplements and updates a staff report prepared in 2011 (Versar, 2011). Other databases and websites were also used to identify additional key information, particularly authoritative reviews. Authoritative reviews for general toxicity and physicochemical information were identified in the following databases using the CAS number for DPHP and synonyms. When relevant data were identified, a PDF of the data file was downloaded from the site. These sites included:

- ANSES Information on Chemicals (https://www.anses.fr/en)
- ChemIDPlus (https://chem.nlm.nih.gov/chemidplus/)
- ECHA Information on Chemicals (https://echa.europa.eu/information-on-chemicals)
- EFSA (https://www.efsa.europa.eu/)
- EPA chemistry dashboard (https://comptox.epa.gov/dashboard)
- EPA (https://www.epa.gov/)
- EPA IRIS (https://www.epa.gov/iris)
- FDA (https://www.fda.gov/)
- Health Canada (https://www.canada.ca/en/health-canada.html)
- IARC (https://www.iarc.fr/)
- INCHEM (http://www.inchem.org/)

- JEFCA (http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/)
- NICNAS (https://www.nicnas.gov.au/)
- NTP (https://ntp.niehs.nih.gov/)
- OECD (http://www.oecd.org/)
- WHO (http://www.who.int/en/)

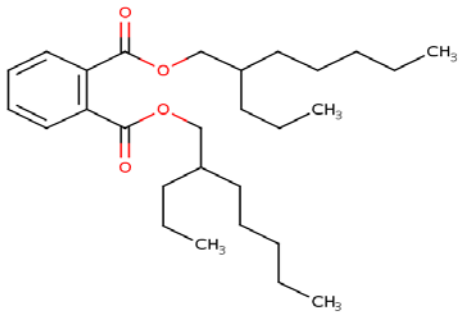
Several new studies were identified in the literature search, including several on toxicokinetics, a short term inhalation study, a new subchronic oral study, a 2-generation study, and several genotoxicity studies, as well as an improved understanding of mode of action (MOA). Several of the key toxicity studies were unpublished and not available as the primary studies. Therefore, these studies were evaluated based on a published review and data compilation (Bhat et al., 2014; ECHA, 2018b).

2 Physico-Chemical Characteristics

DPHP is an *ortho* phthalate with a backbone of C7 branched alcohol with a propyl side chain. DPHP is currently considered to belong to the High Molecular Weight Phthalate Esters (HMWPE) group. DPHP is a specific isomer of di-isodecyl phthalate (DIDP) (NICNAS, 2003). The identity and physicochemical properties of DPHP can be seen in Tables 2.1 and 2.2 (NICNAS, 2003).

Table 1: Physical-Chemical Characteristics of DPHP

Chemical Name	Di(2-propylheptyl) phthalate (DPHP)
Synonyms	Bis(2-propylheptyl) phthalate; di-2-propylheptyl phthalate; phthalic acid, bis(2-propylheptyl) phthalate; phthalic acid, bis(2-propylheptyl) ester; 1,2-benzenedicarboxylic acid, 1,2-bis(2-propylheptyl) ester
Purity/Impurities/Additives	Purity: >99.5% w/w; Impurity: 1,2-Benzenedicarboxylic acid, bis(4-methyl-2-propylhexyl) ester (weight % = 2); Impurity: 1,2-Benzenedicarboxylic acid, 4-methyl-2-propylhexyl 2-propylheptyl ester (weight % =15); Stabilizer: 0.1% Topanol CA; 0.3-0.5% bisphenol A (4,4'-isopropylidenediphenol) (NICNAS, 2003)
CAS Number	53306-54-0

Structure	
Chemical Formula	$C_{28}H_{46}O_4$
Molecular Weight	446.672 g/mol
Physical State	Oily liquid (NICNAS, 2003)
Color	colorless
Density	0.947 g/cm^3
Melting Point	- 45 ºC[a] (EU, 2001, as cited by NICNAS, 2003)
Boiling Point	252.5–253.4 ºC (BASF 2015)
Vapor Pressure	2.07x10^{-7} mm Hg
Water Solubility	8.17x10^{-8} mol/L
Log Kow[b]	10.6-10.8 (calculated, BASF 2015)
Henry's law constant	1.5 x 10^{-7} atm-m^3/mol (calculated)
Flashpoint	229 ℃ (calculated)
BCF	Not located
Source	U.S. EPA (2018a), unless otherwise stated

[a] Listed as the "pour point" by BASF (2015).

[b] K_{ow} is the octanol-water partition coefficient. See Appendix 2 for more detail.

3 Manufacture, Supply, and Use

Manufacture and Supply

Total U.S. manufacture and imports of DPHP was reported to be between 50,000,000 and 100,000,000 pounds (25,000 to 50,000 tons) per year for 2015 (U.S. EPA, 2018b). The overall production and/or imported volume in Europe is between 100,000 and 1,000,000 tons per year (ECHA 2014). DPHP is registered under REACH (Regulation (EC) No. 1907/2006) (Klein et al., 2018). In Europe, HMWPEs (including DPHP, diisononyl phthalate [DINP], DIDP, diundecyl phthalate [DIUP], and 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich [DTDP]) represent approximately 85% of all phthalates produced (DEZA, 2013). The use of DPHP has been growing, and it replaces other linear phthalates as a plasticizer in certain polyvinyl chloride (PVC) applications. The production of DPHP as a proportion of total

phthalate production has increased substantially between 2005 and 2008 (CEH, 2009, as cited by CPSC, 2014).

Use

HMWPEs, such as DPHP, are used as industrial chemicals, often as an additive to impart flexibility to PVC resins. The PVC is then made into end-use products using extrusion, calendaring, and injection molding processes (NICNAS, 2003). HMWPEs are also used as a synthetic base stock for lubricating oils (OECD, 2004). ECHA (2014) notes that DPHP has widespread uses and is an ingredient in consumer preparations such as paints and adhesives; in plastic consumer articles, including toys and childcare articles; and in medical devices.

Consumer uses include as an ingredient or additive in adhesives and sealants; building and construction materials; electrical and electronic products; fabric, textiles, and leather products; floor coverings; furniture and furnishings; lubricants and greases; paints and coatings; personal care products; plant and rubber products; footwear; and paper and cardboard products (PubChem, 2018; ECHA, 2018a). The National Library of Medicine Household Substances Database (NLM, 2018) lists a number of polyurethane sealants containing DPHP that are used on masonry, windows, doors, siding, and roofing; and a concrete filler and leveler made with DPHP. The DPHP content of these household products is generally 5-10% (NLM, 2018).

Commercial uses of DPHP include auto undercoating and interiors, building materials, wires, cables, carpet backing, pool liners, and roofing membranes or tarpaulins (BASF, 2015; CPSC, 2011; NICNAS, 2003; all as cited by Klein et al., 2016). Typically, the content of DPHP in end-use products ranges between 30% and 60% (w/w) (NICNAS, 2003, as cited by Klein et al., 2016).

4 Toxicokinetics

No toxicokinetic studies of DPHP have been conducted via the inhalation or dermal routes. However, the observation of liver changes in rats exposed via inhalation to DPHP aerosol for 5 days (Anonymous, 2013, as cited by ECHA, 2018b) indicates that inhaled DPHP can be absorbed and systemically distributed. Several high-quality oral toxicokinetic studies are available for DPHP in humans and rats, but none of the studies evaluated all aspects of toxicokinetics (absorption, distribution, metabolism, and excretion), and no study conducted a mass balance analysis. Instead, the studies focused on analyzing DPHP and its metabolites in blood and urine.

Quantitative data were not available on the degree of gastrointestinal absorption in the rat. In humans, total urinary excretion of oral DPHP, including metabolites, varied considerably by study. Klein et al. (2018) administered DPHP to six male volunteers as an emulsion in an aqueous saccharose (sucrose) solution after breakfast, and reported only 6.1% excretion within

46 hours of dosing. In contrast, other studies reported 24.7% excretion after 48 hours (about 0.5%/hour) in five male volunteers administered DPHP dissolved in ethanol and mixed in an edible waffle cup (Leng et al., 2014) and 34% after 61 hours (vehicle and number of subjects not reported) (Wittassek and Angerer, 2008). The remainder of the administered dose was likely in the feces, and presumably reflects unabsorbed DPHP, although information on biliary excretion was not available. Differences in the degree of (presumed) absorption may have been due to differences in factors such as the dose vehicle and the gastrointestinal tract content. These studies are discussed in further detail below, in the context of DPHP metabolism. No study investigated distribution to any tissue besides the blood, and it is not known whether DPHP or its metabolites cross the placenta.

Metabolism of DPHP is similar to that of DEHP (Wittassek and Angerer, 2008; Leng et al., 2014; Klein et al., 2018). Ester cleavage of the diester results in formation of the mono-ester, followed by oxidation of the remaining alkyl side chain, and potential glucuronidation. (See Figure 1.) However, differences exist between rats and humans in the relative amount of DPHP and metabolites in the blood, in the amount of glucuronidation, and in the relative amount of omega-1 and omega oxidation.

Klein et al. (2016) investigated the toxicokinetics of DPHP in male Wistar (Crl:WI(Han)) rats (3/dose/time point) in a study designed to improve the interspecies kinetic extrapolation. The rats were administered a single oral gavage dose of DPHP as an aqueous emulsion in a 70% saccharose solution, at 0.7 or 100 mg/kg. DPHP was administered as Palatinol®10-P (98% pure) at the high dose, and ring-deuterated DPHP (DPHP-d4) was used for the low dose, in order to ensure adequate sensitivity to observe metabolites. Blood was collected at frequent intervals through 24 hours post-dosing. Large inter-individual variation was observed, but it was still possible to obtain meaningful kinetic parameters. The peak blood concentration for the 100 mg/kg dose group occurred at about 1.5 hours after dosing; blood concentrations at the low dose were too close to the limit of quantification to fit a curve and estimate the peak time. Distribution to other tissues was not evaluated in this study, and excreta were not assessed. The authors identified the metabolites in the blood and proposed the following metabolic pathway. (See also Figure 1). DPHP is hydrolyzed to mono-(2-propylheptyl) phthalate (MPHP), which can be further metabolized to mono-(2-propyl-6-carboxyhexyl) phthalate (cx-MPHP) or to mono-(2-propyl-6-hydroxyheptyl) phthalate (OH-MPHP). The OH-MPHP can be further oxidized to mono-(2-propyl-6-oxoheptyl) phthalate (oxo-MPHP). Both oxo-MPHP and cx-MPHP can be glucuronidated prior to excretion. The peak blood concentrations of MPHP, OH-MPHP, and oxo-MPHP were reached at about 1 hour after dosing, and that of cx-MPHP at about 3 hours after dosing.

The study authors determined the half-life in blood and the area under the concentration-time curve (AUC) for DPHP and its metabolites at the high and low doses (Table 2). As shown in

Table 2, the AUC for the free and total compound (including glucuronidated compound) were nearly identical, indicating very little glucuronidation. This similarity occurred at both the low and high doses, indicating that the lack of glucuronidation does not result from saturation of glucuronosyl transferase activity. The AUC of the parent DPHP was very low relative to that of the metabolites, indicating rapid metabolism and low bioavailability of the parent compound. The study authors suggested that this low bioavailability of DPHP relative to that of phthalates with straight chain lengths of the alcohol moieties of C_3-C_7 could be one reason that phthalates with longer straight chains were not reproductive toxicants, while phthalates with shorter chains were. The tissue primarily responsible for the first-pass metabolism of DPHP is not known, but the authors suggested that the initial hydrolysis to MPHP occurs in the small intestine, by analogy to diethylhexyl phthalate (DEHP). Saturation of this hydrolysis was occurring at the high dose in this study, based on the 2.5- to 2.9-fold lower normalized AUCs for the metabolites at the high dose compared to the low dose. At the high dose, the AUC for cx-MPHP was comparable to the total of the AUC for OH-MPHP and oxo-MPHP, suggesting equal amounts of metabolism via the two pathways.

TABLE 2. AUC and half-lives of the elimination phases of DPHP and its metabolites in blood of rats after single oral administration (Klein et al., 2016)

Compound	Half-life [h][a]				AUC [nmol·h/l per µmol DPHP(-d4)/kg b.w.][b]			
	Total Compound[c]		Free Compound		Total Compound[c]		Free Compound	
	0.7 mg/kg	100 mg/kg	0.7 mg/kg	100 mg/kg	0.7 mg/kg	100 mg/kg	0.7 mg/kg	100 mg/kg
DPHP	-	-	n.d.	2.4	-	-	n.d.	13
MPHP	2.5	3.0	2.3	3.0	194	78	185	73
OH-MPHP	3.0	4.6	3.1	4.5	183	72	179	70
Oxo-MPHP	3.3	4.9	3.2	4.7	100	36	99	34
cx-MPHP	n.d.	8.2	n.d.	8.1	n.d.	142	n.d.	137

n.d.: not determined

[a] Derived from the exponential functions fitted to the data

[b] Area under the concentration-time curve calculated for $t \rightarrow \infty$, normalized for the DPHP dose as derived from the exponential functions fitted to the data

[c] Sum of free and glucuronidated compound.

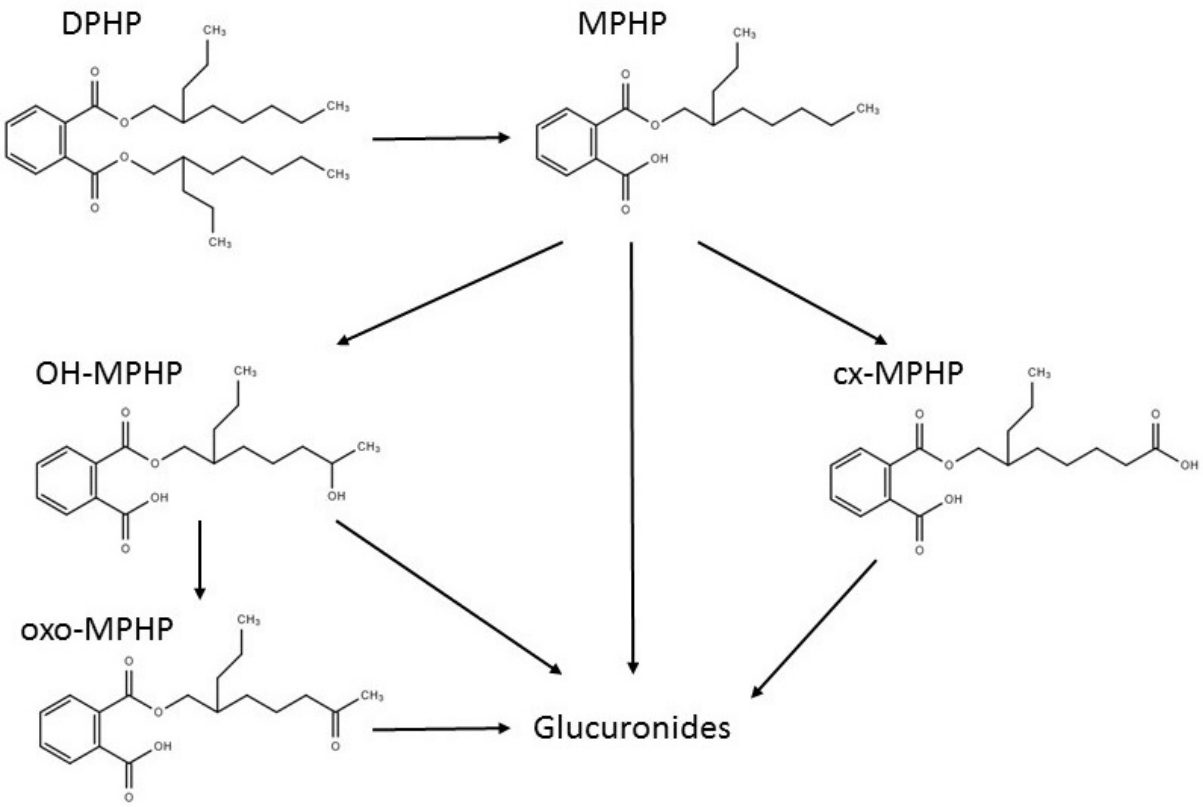


Figure 1. Metabolic pathway of DPHP in rats (adapted from Klein et al., 2016).

A number of studies investigated levels of DPHP and its metabolites in the blood and urine of volunteers following intentional exposure. These studies were conducted either in support of development of biomonitoring methods (see Section 6), or to aid in comparison of kinetics in humans and experimental animals (Klein et al., 2016, 2018). In a study with poor documentation, Wittassek and Angerer (2008) reported that 61 hours after oral administration of an unspecified dose of DPHP, approximately 34% of the dose was excreted in the urine, mainly as OH-MPHP (~ 17%) and oxo-MPHP (~ 16%), with a lesser amount as cx-MPHP (< 5%). The simple monoester in the urine (MPHP) accounted for <1% of the administered dose. The study did not report the dose, and the study population was not clearly identified, although the text noted the testing of a single male volunteer with another phthalate. Leng et al. (2014) stated that the dose in the Wittassek and Angerer (2008) study was 98 mg DPHP ingested during breakfast, but the basis for that statement is unclear.

A similar distribution of metabolites was reported by Leng and Gries (2017) from a biomonitoring study of the urine from 51 German volunteers. Of the 51 samples, 20 had concentrations greater than the limit of quantification (LOQ) for OH-MPHP, and 17 had concentrations greater than the LOQ for oxo-MPHP. In contrast, none of the samples had concentrations of cx-MPHP exceeding the LOQ. Thus, unlike the rat, where comparable

amounts of metabolism went through each of the two oxidative pathways, metabolism in humans appears to favor omega-1 oxidation to OH-MPHP over formation of cx-MPHP.

In support of the development of a biomonitoring program, Leng et al. (2014) orally administered 50 mg ring-deuterated DPHP-d4 mixed in an edible waffle cup during breakfast, to five healthy male volunteers (based on individual body weights, actual doses were 0.54-0.66 mg/kg). All urine was collected for a 48-hour period, and concentrations of the metabolites OH-MPHP, oxo-MPHP, and cx-MPHP were measured. The peak urinary concentration was seen at about 3.5 hours for OH-MPHP and oxo-MPHP, and at about 4 hours for cx-MPHP. The mean excretion half-lives and standard deviations were 6.51 ± 1.64, 6.87 ± 1.63 and 8.16 ± 0.67 hours for oxo-MPHP, OH-MPHP, and cx-MPHP, respectively. The study authors also calculated the molar excretion fraction in % of oral dose (fractional urinary excretion - fue) for each of the three metabolites at 0-24 and 24-48 hours (Table 3). The predominant metabolites were OH-MPHP and oxo-MPHP, with cx-MPHP accounting for only about 2% of the total urinary excretion at 24 and 48 hours. Total urinary excretion of the three metabolites accounted for 22.94% of the oral dose in the first 24 hours and 24.70% in the first 48 hours. Additional details are presented in Table 3. The authors described the excretion as rapid and following an apparent one-phasic elimination pattern, but only about 25% of the administered dose was excreted within 48 hours, and all three metabolites were still detectable at 48 hours post-dosing. Neither the parent DPHP nor the monoester were measured, although the monoester was expected to account for a small percent of the urinary metabolites, based on the results of Wittassek and Angerer (2008). The metabolites identified in the *in vivo* study are supported by an *in vitro* study reported as supplemental data to a biomonitoring study. In that study, Alves et al. (2017) reported the *in vitro* metabolism of DPHP to MPHP, and of MPHP to OH-MPHP. The provided information was not clear on which chemicals were tested in which metabolic systems; possible systems included human liver microsomes and human intestinal microsomes.

Table 3: Elimination half-lives and times of maximum urinary excretion for the three oxidized DPHP metabolites after oral dosage (Leng et al., 2014)

Parameter	Mean t_{max}±SD (h)	Mean $t_{1/2}$±SD (h)	Fractional Urinary Excretion 0-24 hours (% dose)	Fractional Urinary Excretion 0-48 hours (% dose)
oxo-MPHP	3.65 ± 1.31	6.51 ± 1.64	12.61 ± 3.90	13.52 ± 4.04
OH-MPHP	3.65 ± 1.31	6.87 ± 1.63	9.91 ± 3.45	10.70 ± 3.61
cx-MPHxP	4.05 ± 1.39	8.16 ± 0.67	0.42 ± 0.11	0.48 ± 0.13
Total of three metabolites			22.94 ± 7.33	24.70 ± 7.64

SD = Standard deviation

Klein et al. (2018) evaluated the kinetics of DPHP metabolism and excretion in six healthy male volunteers, with the goal of improving the comparison between rats and humans. DPHP (Palatinol®10-P, purity 98%) or ring-deuterated DPHP was administered orally in an aqueous saccharose solution (70% w/v) at a dose of 0.738 ± 0.056 mg/kg. The dose was chosen to be comparable to the low dose administered to rats in the Klein et al. (2016) study. The subjects consumed breakfast prior to dosing, in order to stimulate intestinal lipase secretion. Blood was collected 30 minutes before dosing and at frequent intervals after dosing, through 24 hours. Total urine was also collected frequently, through 46 hours post-dosing. The parent compound appeared in the blood later than the metabolites, with a lag time of about 2 hours. The authors interpreted the rapid appearance of MPHP in the blood as indicating that systemic concentrations of MPHP are initially determined by its formation in the gastrointestinal tract. There was considerable inter-individual variability in the kinetic profiles, particularly in the AUCs for DPHP (as reflected in the large standard deviations); half-life for elimination from blood of DPHP and the metabolites was 4.1-4.6 hours, depending on the compound. The AUC in blood for the parent and metabolites is shown in Table 4. The AUC was largest for the parent compound, followed by the monoester MPHP, with smaller amounts of the two secondary metabolites OH-MPHP and oxo-MPHP. The AUC of OH-MPHP plus that of oxo-MPHP was similar to that of MPHP, indicating that metabolism of MPHP is primarily via omega-1 oxidation, rather than to cx-MPHP. Urinary excretion half-lives for MPHP, OH-MPHP, and oxo-MPHP were slightly more than 5 hours; excretion of cx-MPHP was slower, with a half-life of 8.7 hours.

On average, across the six volunteers studied, only 6.1 ± 3.4 % (range 1.93-10.5%) of the administered dose was excreted in the urine; the authors suggested that the remainder of the dose was excreted in the feces. Of the total excretion observed within 46 hours, 90% had occurred within the first 22 hours. The most abundant metabolites were oxo-MPHP and OH-MPHP (60% and 37% of total urinary amount, respectively), with MPHP and cx-MPHP contributing much smaller amounts. The 22-hour urinary excretion of OH-MPHP correlated well with AUCs of MPHP, OH-MPHP, and oxo-MPHP in the blood, indicating that OH-MPHP would be a good biomarker for internal dose. The correlation was weaker between levels of oxo-MPHP in urine and blood levels of the three metabolites.

Comparing the internal dose ($AUC_{0-\infty}$) in this human study to rats receiving the same oral dose of DPHP (0.7 mg/kg, Klein et al., 2016), the authors noted that DPHP in rat blood could not be quantified, but DPHP represented the highest AUC in human blood. For the metabolites, the $AUC_{0-\infty}$ was 3.2-fold (MPHP), 1.6-fold (OH-MPHP), and 4.4-fold (oxo-MPHP) higher in humans than in rats. Apparently based on the large DPHP AUC in humans, the authors concluded that the AUCs of the DPHP metabolites in humans are probably determined primarily by the metabolism of systemic DPHP, while in rats (with insignificant DPHP in the blood), the AUCs of the metabolites appears to be determined by the absorption of intestinally-formed MPHP. Similar differences were noted between rats and humans for DEHP (Kessler et al., 2012,

as cited by Klein et al., 2018). Inter-species differences in the degree of glucuronidation were also noted, with most of the metabolites existing in the un-glucuronidated (free monoester) state in rats, and the amount of free monoester metabolite decreasing with the degree of oxidation in humans (Table 4). If the active form(s) of DPHP are identified, the relative AUC in rats and humans could be used to refine the interspecies extrapolation.

Table 4. AUC of DPHP and its metabolites in blood of volunteers administered single oral dose. (Klein et al., 2018)

Compound	AUC, total compound[a] (nmol*h/L per µmol DPHP)/kg	**AUC,** free **compound** (% total compound)
Mean AUC_{0-24} ± SD		
DPHP	961 ± 1048	--
MPHP	643 ± 426	61 ± 7.7
OH-MPHP	279 ± 175	22 ± 7.6
Oxo-MPHP	366 ± 329	4.3 ± 1.1
Mean $AUC_{0-\infty}$[b]		
DPHP	844	--
MPHP	618	65
OH-MPHP	291	22
Oxo-MPHP	440	5.1

[a]Sum of free and glucuronidated compounds

[b]Calculated based on curve parameters

Shih et al. (2018) identified additional DPHP metabolites as part of an attempt to identify additional potential DPHP exposure biomarkers for use in metabolomics. Metabolites were initially identified based on their formation in vitro by human liver S9, and confirmed based on their dose-dependent formation in rats dosed orally (75-1200 mg/kg). The study authors identified the four metabolites noted previous (MPHP, OH-MPHP, oxo-MPHP, and cx-MPHP), and 13 tentative novel biomarkers. Of these, four tentative novel biomarkers were verified as having structures related to DPHP, and three tentative novel biomarkers were considered suitable potential biomarkers, based on their higher peak intensity ratios compared with the previously-reported DPHP metabolites. Two of these compounds were isomers of cx-MPHP, and the third appeared to have been formed from oxo-MPHP.

5 Hazard Information[1]

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

No deaths were reported in a group of five male and five female Sherman-Wistar rats treated with a single gavage dose of 5000 mg/kg of DPHP (91.3% pure; 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl phthalate) and observed for 14 days, indicating an oral LD_{50} of >5,000 mg/kg (Nuodex, Inc., 1979a, as cited by Versar, 2011). No unusual behavioral signs were noted and gross necropsy of the rats was unremarkable. No other relevant studies were located.

5.1.2 Acute Dermal Toxicity

A dermal LD_{50} >2,000 mg/kg was reported, based on an experiment in which 2000 mg/kg DPHP (91.3% pure; 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl phthalate)) was applied to a clipped and abraded area of the back of three male and three female albino rabbits for 24 hours (Nuodex, Inc., 1979b, as cited by Versar, 2011). The application site was covered, and excess material was removed after the 24-hour exposure period. No clinical signs were noted during the 14-day observation period, and no animals died during this time. Gross necropsy was unremarkable. No other relevant studies were located.

5.1.3 Acute Inhalation Toxicity

A group of five male and five female albino rats (strain not specified) was exposed whole-body to 20.5 mg/L (the maximum concentration that could be attained) of DPHP (91.3% pure; 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl phthalate) as an aerosol (particle diameter = 3–5 microns) for 1 hour and observed for 14 days (Nuodex, Inc., 1979c, as cited by Versar, 2011). The rats were wet, ruffled, agitated, and raspy sounding immediately after exposure, but appeared normal 24 hours after exposure. No rats died during the study and gross necropsy did not reveal significant alterations. This study suggests a 1-hour LC_{50} of >20.5 mg/L in rats. No other relevant inhalation studies were located. Assuming toxicity is related to the product of concentration and time (C x t), this study would indicate a 4-hour LC_{50} of > 5 mg/L.

5.1.4 Irritation/Sensitization

Nuodex, Inc. (1979d, as cited by Versar, 2011) reported that application of 0.5 g of DPHP (91.3% pure) to intact or abraded areas on the clipped back of six albino rabbits (strain not

[1] Where available, this report provides significance level p values in all sections. However, secondary references used as data sources often reported only that a change was significant without reporting the p level, or just reported an effect without noting if it was statistically significant. If no p level is reported in this text, the p level was not available in the cited secondary reference, but the significance is presumed to be statistical.

specified) under occlusion for 24 hours did not cause irritation. Observations were conducted at 24 and 72 hours. None of animals showed any evidence of erythema or edema at either time point. In another study (BASF, 2002a, as cited by Versar, 2011 and ECHA, 2018b), 0.5 mL DPHP was applied to the skin of New Zealand White rabbits (one male and two females) under "semi-occlusive" conditions for 4 hours, after which the site was washed with Lutrole:water (1:1). Irritation was evaluated at 1, 24, 48, and 72 hours. There are some slight variations in the irritation scores reported by different secondary sources, although there is agreement that the irritation was slight. BASF (2002a, as cited by NICNAS, 2003, as cited by Versar, 2011) reported a Primary Irritation Index of 0.25, while ECHA (2018b) reported an erythema score of 1 (on a scale of 0 to 4) in all animals at 1 hour, an average erythema score (24-72 hours) of 0.3 in one animal, and an overall average erythema score of 0.1. None of the rabbits exhibited any edema at any time point. In guinea pigs (five per sex) given 10 repeated 24-hour applications of 500 mg of DPHP (91.3% pure) to intact skin under occlusion at 48-hour intervals, several of the animals tested showed evidence of minimal erythema after applications 5–10 (Nuodex, Inc., 1979e, as cited by Versar, 2011).

Instillation of 100 mg DPHP (91.3% pure) into the right eyes of six albino rabbits (the left eyes served as untreated controls) produced no evidence of ocular irritation, based on examinations of the cornea, iris, and conjunctiva of the unwashed eyes at 1, 24, 48, and 72 hours, and 5 and 7 days after instillation of the chemical (Nuodex, Inc., 1979f, as cited by Versar, 2011). In another study, 0.1 mL DPHP (purity not available) in the eye for 24 hours prior to washing was slightly irritating to the eye of three New Zealand White rabbits. Slight to moderate conjunctival redness were seen in the first 24 hours, accompanied by slight discharge at 1 hour. All reactions were reversible within 48 hours. The average score for 24-72 hours was 0.0 for corneal opacity, iris, and chemosis, and 0.3 for conjunctival redness (BASF, 2002b, as cited in NICNAS, 2003 and ECHA, 2018b).

DPHP was also tested for skin sensitization in guinea pigs. In the repeated dermal application study described above (Nuodex, Inc., 1979e, as cited by Versar, 2011 and ECHA, 2018b), the 10^{th} application was followed by a 2-week rest period. At that time, 24-hour challenge applications of 0.5 g were placed at skin sites different from the original sites. The challenge sites were examined for evidence of irritation after 24 and 48 hours. There was no evidence of erythema or edema at either time point in the challenge test. This result is supported by the results of a quantitative structure activity relationship (QSAR), which predicted a negative sensitization potential for DPHP, MPHP, and the putative metabolite 2-propylheptanol.

5.2 Repeated Dose Toxicity

Overview

In order to aid in understanding the spectrum of effects resulting from repeated exposures to DPHP, this section provides a brief overview of the primary observed health effects and their human relevance. Due to the importance of understanding mode of action (MOA) in order to evaluate human relevance, MOA is reviewed here briefly, and discussed in greater detail in Section 5.8. The primary targets of repeated exposures to DPHP are the liver, thyroid and pituitary. Like many other phthalates (reviewed by CPSC, 2014), DPHP is a peroxisome proliferator. Binding to peroxisome proliferator-activated receptor α (PPARα) has not been investigated for DPHP, but DPHP studies consistently show an increase in cyanide insensitive palmitoyl CoA oxidase (PCO) activity, a marker for peroxisome proliferation. Bhat et al. (2014) also hypothesized that liver effects from DPHP exposure may be occurring through the Constitutive Androstane Receptor (CAR). Peroxisome proliferators, such as DEHP, cause liver-related changes that include increased relative liver weights due to hepatocellular hypertrophy and proliferation, increased replicative DNA synthesis, increased number and size of peroxisomes (ultrastructural effects), and induced peroxisomal and microsomal fatty acid-oxidizing enzymes that lead to decreased serum triglycerides, among other changes. In humans, activation of PPARα does not lead to increased relative liver weights, oxidative enzyme induction or other responses typically associated with sustained PPARα activation observed in wild-type mice (Corton et al., 2018). CPSC (2014) raised some questions about this conclusion regarding human relevance, but those concerns were addressed by Felter et al. (2018). The weight of evidence supports the conclusion that adverse effects related to a PPARα MOA is either “not relevant” or “unlikely to be relevant” in humans (Felter et al., 2018). The spectrum of liver effects should also be considered, even in determining the adversity to rodents. Increases in liver weight of 150% or less, in the absence of degenerative or necrotic liver changes at any dose or duration, are considered adaptive, rather than adverse (Hall et al., 2012). Similar conclusions were reached by the U.S. EPA (2002).

The liver metabolic enzymes induced by peroxisome proliferators in rodents can include uridine diphosphate glucuronyl transferase (UGT) (Barbier et al., 2003), which can lead to increased hepatic clearance of the thyroid hormones T3 and T4. This increased T3 and T4 clearance can lead to a negative feedback to the pituitary and hypothalamus, resulting in compensatory increase in thyroid stimulating hormone (TSH), followed by thyroid hypertrophy and ultimately thyroid hyperplasia and tumors in rodents. This MOA is also considered not relevant to humans for tumorigenesis, but it is relevant for neurodevelopmental effects (Dellarco et al., 2006). However, as discussed further in Section 5.8, although this MOA for DPHP thyroid effects are plausible, the key events have not been established, and other (human-relevant) MOAs are also possible.

Short-term Inhalation Study

One repeated dose study is available via the inhalation route (Anonymous, 2013, as cited by ECHA, 2018b). In this study, groups of 10 male Wistar rats were exposed to 0, 50, 250, or 1000 mg/m^3 DPHP aerosol (MMAD 1.4-2.2 µm; GSD 2.1-2.9 µm) for 6 hours/day for 5 consecutive days. There were no clinical signs of toxicity, and no effect on mean body weight or on hematology. Globulin and total protein levels were decreased and cholesterol levels increased at the high concentration. These changes were considered adverse, but the degree of change was not reported. The primary target of toxicity was in the respiratory tract. Single mucous cells in the maxillary sinus of the nasal cavity were seen at the low concentration in the absence of inflammation, and this change was considered adaptive. At the mid concentration, absolute and relative lung weight were increased (by 9% and 7%, respectively), accompanied by granulomatous inflammation of the lungs (2/10), alveolar histiocytosis of the lungs (10/10), epithelial hypertrophy/hyperplasia of the bronchioles, and the same nasal effects as seen at the low concentration. At the high concentration, lung weight was increased by 37%, and the same pathology endpoints as seen at the mid-concentration were observed, with increased severity. In addition, there was hypertrophy/hyperplasia of mucous cells and respiratory tract-related lymph nodes. The NOAEC was 50 mg/m^3 and the LOAEC was 250 mg/m^3 for effects on the respiratory tract.

The liver was also a target at the high concentration. Absolute and relative liver weight were increased by 30%, and there was slight diffuse hepatocellular hypertrophy in all high-concentration males. These changes are considered adaptive and not adverse.

Short-term Oral Study

One short-term oral repeated dose study is available. In this range-finding study, male and female Wistar rats (number unspecified) were provided DPHP at 0, 1000, 10,000, or 20,000 ppm in the diet for 2 weeks (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b[2]). Bhat et al. (2014) reported that increased PCO activity was seen at the mid dose, calculated to correspond to 920 mg/kg-day in males and 1020 mg/kg-day in females. Additional details on the study design or results were not available.

Subchronic Oral Study in Wistar rats

Based on the results of the 2-week study, BASF AG (1995b, as cited by Bhat et al., 2014) conducted a 13-week study (OECD Guideline 408) in which 6-week-old male and female Wistar rats (10/group) were fed DPHP (98.7% purity) at 0, 500, 2500 or 15,000 ppm. The calculated

[2] ECHA summarized this study as part of the rationale for the dose selection for the 13-week (BASF, 1995b), rather than as an independent study, and so few study details are available.

dose was 0, 36, 181 or 1187 mg/kg-day for males and 0, 42, 211 or 1344 mg/kg-day for females, based on actual amount ingested. Bhat et al. (2014) calculated human equivalent doses (HEDs) of 0, 10, 51, and 331 mg/kg-day (males) and 0, 11, 53, and 328 mg/kg-day (females), based on $BW^{3/4}$ scaling using mean body weight at sacrifice for the rats and 70 kg for humans. The endpoints evaluated included liver PCO activity, clinical chemistry, urinalysis and hematology parameters, ophthalmoscopic examination, and complete histopathology and well as organ weights of major organs and reproductive organs.

Terminal body weight was significantly ($p<0.05$) decreased by 8% in females and 6% in males at the high dose, but food consumption was not affected. This change is below the threshold for adversity. Liver effects were consistent with those expected for a peroxisome proliferator. PCO was markedly and significantly ($p<0.01$) increased in both sexes at the high dose, and significantly increased ($p<0.05$) in females at the mid dose. Similarly, absolute liver weight was significantly ($p<0.01$) increased by more than 50% at the high dose in both sexes, and there was also a significant (20%, $p<0.05$) increase in mid-dose females. All high-dose animals had diffuse hypertrophy of the liver, compared to none of the controls. The liver changes were considered adaptive and therefore the summary in Table 5 depicts the highest dose in each sex as a NOAEL..

There was a significant *decrease* in absolute adrenal weight (16%, $p < 0.05$ in males; 6% in females, $p > 0.05$) at the high dose, but this change was not accompanied by associated histopathology, and does not appear to have been considered adverse in the available reviews (Bhat et al., 2014; NICNAS, 2003). However, this decrease in males is larger than the corresponding decrease in body weight, and so is potentially adverse. Relative kidney weight (14% in males, $p<0.01$, 10% in females, p value not available) and relative brain weight (10% in males and 8% in females) were increased at the high dose. Most of the increase in relative kidney weight can be attributed to the decreased body weights, and is likely not adverse. The increased relative brain weights likely reflects the decreased body weights, since brain weight is generally unaffected by changes in body weight.

Thyroid weight and thyroid hormone levels were not measured, but thyroid hypertrophy was reported in mid- and high-dose males and females. These changes are consistent with increased thyroid hormone clearance secondary to liver enzyme induction, followed by compensatory changes in the thyroid. Male rats also had an increase in basophilic cells in the anterior part of the pituitary gland (3/10 at the mid dose, 8/10 at the high dose). These cells produce thyroid stimulating hormone, which activates the thyroid to release more T_3 and T_4. For both the thyroid and pituitary, the low dose (36 mg/kg-day in males, 42 mg/kg-day in females) was a NOAEL in rats. The effects on the thyroid and pituitary are potentially secondary to increased thyroid hormone clearance and thus potentially not relevant to humans, but the MOA had not been demonstrated for DPHP, and so these effects are assumed to be relevant.

Bhat et al. (2014) reported that a significant increase in alkaline phosophatase in high-dose males and females was also observed in this study, and stated that the increases were attributed to potential bone toxicity, since they were accompanied by decreases in serum calcium and increases in serum inorganic phosphorus. However, the changes in calcium and phosphorus were not reported by ECHA (2018b), and were not accompanied by changes in femoral bone marrow histopathology.

Hemoglobin and hematocrit were significantly ($p<0.05$ and $p<0.01$, respectively) decreased in high-dose males, and hemoglobin ($p<0.01$) and mean corpuscular hemoglobin ($p<0.05$) were significantly decreased in high-dose females, but the changes were <10% and there was no dose-response. Platelets were significantly ($p<0.01$) increased by 20% in high-dose males but there was no increase in females. Triglycerides were significantly decreased (by 43%) in high-dose males, consistent with the effects of a PPARα inducer; glucose was also significantly decreased (by 12.5%) in high-dose females.

Several assessments have used the subchronic study in Wistar rats as the basis for developing exposure limits. Klein et al. (2016) and Apel et al. (2017) noted the development of a German human biomonitoring assessment value (HBM) based on a NOAEL of 39 mg/kg-day, rounded to 40 mg/kg-day (based on averaged male and female doses) for effects on the thyroid and the pituitary gland. NICNAS (2003) also used a NOAEL of 39 mg/kg-day from this study for evaluation of margins of exposure (MOEs), based on liver and thyroid effects. Bhat et al. (2014) agreed that the NOAEL in this study was 36 mg/kg-day in males and 42 mg/kg-day in females, based on liver, thyroid and pituitary effects. They calculated a $BMDL_{(HED)}$ of 6.1 mg/kg-day as the lowest BMDL from this study, based on thyroid hypertrophy in males. However, Bhat et al. (2014) derived their RfD based on thyroid effects in the 2-generation study (BASF AG, 2009, see Section 5.4), due to the longer duration of that study and the similar $BMDL_{(HED)}$ of 10 mg/kg-day.

Subchronic Study in Alpk:APfSD rats

A second subchronic feeding study was conducted in rats, but the documentation available for this study is much more limited, and it was not conducted according to testing guidelines. Union Carbide Corporation (1997, 1998) provided a brief summary of preliminary findings of a 90-day study in Alpk:APfSD rats (12/sex/group) that were fed a diet containing 0, 500, 5000, or 12,000 ppm DPHP for 14 weeks. This study is also summarized by ECHA (2018b) and Bhat et al. (2014). The corresponding doses were reported as approximately 0, 40, 420, and 1000 mg DPHP/kg-day, based on measured food consumption and body weight. The study included hematology and clinical chemistry evaluation as well as organ weight evaluation and histopathology of an unspecified list of organs and tissues. The study also included recovery

groups that were fed 0 or 12,000 ppm in the diet for 90 days and then held for 4 weeks for observation before being sacrificed.

Body weight was significantly decreased in the high-dose rats, with decreases in terminal body weights (relative to controls) of 23% and 19% in males and females, respectively. The difference in body weight gain was reportedly partially resolved following the 4-week recovery period. The reduced weight gain at the high dose was accompanied by a decrease in food consumption, the magnitude of which was not specified. A smaller decrease in terminal body weight of 6% was reported in mid-dose males, but no further details were available. The LOAEL for decreased body weight in both sexes was 1000 mg/kg-day.

Decreases (of unspecified magnitude) were seen in red blood cell count, hemoglobin, and hematocrit, and increased platelet counts in male rats at the mid dose and higher, and in female rats at the high dose. Because hematology endpoints often have little variability, and so can have statistically significant changes that are not biologically meaningful, no assessment is possible on the adversity of the hematology changes or adverse effect levels. In addition, the subchronic study in Wistar rats (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b) reported statistically significant decreases in hematology parameters that were not biologically meaningful.

Effects on the liver were consistent with peroxisome proliferation. Peroxisome enzyme levels (not further identified) were increased in all treatment groups, and PCO was increased at the mid and high doses. Liver weight (not reported whether absolute or relative) was also increased in all treatment groups. Decreases in plasma cholesterol and triglyceride were also observed, and are consistent with peroxisome proliferation, although the affected doses were not reported. Further details were not provided, and so a clear effect level cannot be identified. In addition, the increased liver weight was adaptive and therefore the summary in Table 5 depicts the highest doses in each sex as a NOAEL.

Histological examination of the adrenal glands revealed a “characteristic vacuolization” of the *zona glomerulosa* in both sexes and in all treatment groups. The severity of the lesion was dose-related; it was described as minimal at the low dose, slight at the mid dose, and moderate at the high dose. Clinical chemistry tests showed decreased plasma sodium and increased plasma potassium in the high-dose males and females. Union Carbide Corporation (1998) noted that the affected part of the adrenal gland is associated with synthesis of several steroid hormones, including aldosterone, a hormone involved in regulation of sodium balance. The authors hypothesized that increased liver metabolism related to the peroxisome proliferation resulted in increased clearance of aldosterone, with the associated changes in the adrenal gland and clinical chemistry. Although this MOA is plausible, no precedent was found in the literature, and the available data are insufficient to support the hypothesis. These results suggest that the low dose

of 40 mg/kg-day was a LOAEL for effects on the adrenal gland possibly secondary to peroxisome proliferation.

Overall, interpretation of this study is limited by the limited data provided. ECHA (2018b) identified a NOAEL of 40 mg/kg-day for males and females, based on body weight changes, hematology, clinical chemistry, organ weights and histopathology, but it is not clear how adversity was evaluated for each endpoint.

5.3 Chronic Toxicity/Carcinogenicity

No chronic studies were located for DPHP. ECHA (2018b) noted that oral exposure to the related compound DINP resulted in increased liver tumors in rats and mice. Similarly, an increased incidence of liver tumors are also seen in rats and mice exposed to the related chemical DEHP (reviewed by ATSDR, 2002). For both chemicals, the liver tumors are considered to be due to peroxisome proliferation, a mode of action not likely to be relevant to humans (Klaunig et al., 2003; Felter et al., 2018).

5.4 Reproductive Toxicity

In a 2-generation study (OECD Guideline 416), Wistar rats (25/sex/dose) were fed "Palatinol 10-P or DPHP" (99.6% purity) in the diet at target doses of 0, 40, 200, or 600 mg/kg-day, beginning at 5 weeks of age (BASF AG, 2009, as cited by Bhat et al., 2014 and ECHA, 2018b). The amount of DPHP in the feed was adjusted on a weekly basis based on body weight and feed consumption, to maintain a constant intake of DPHP. Exposure was continuous in feed, in utero or via mother's milk through the F2 generation. In addition to standard reproductive toxicity parameters, the study evaluated hematology endpoints and clinical chemistry.

Body weights were statistically significantly decreased (by more than 10%) at the high dose in both parental generations, and so the NOAEL for decreased body weight was 200 mg/kg-day. Statistically significant decreases in red blood cells, hematocrit, and hemoglobin were seen in both sexes in both the F0 and F1 generations. While these changes were clearly treatment-related, no information on the magnitude of the response was available, and Bhat et al. (2014) did not consider the changes adverse. Other changes occurred only in one generation and were considered incidental.

A variety of changes related to the liver were noted, most of which were related to enzyme induction. The sole exception was increased serum alkaline phosphatase (ALP), which was significantly ($p<0.01$) increased by more than 30% (but less than a doubling) in high-dose males and females of both generations, and in mid-dose males of both generations. The increases in ALP were not supported by increases in serum transaminases. Although some statistically

significant increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were seen at the high dose, the magnitude of the changes were considered marginal. Absolute and relative liver weight were also significantly increased ($p<0.01$) in both sexes and both generations. Hepatocyte hypertrophy was also increased in both sexes and generations at the high dose, and in mid-dose males in both generations. The increased liver weight and hypertrophy were considered adaptive, the change in ALP was less than that considered adverse, and serum transaminase levels were not considered indicative of liver damage. Therefore, no adverse effect level was identified for the liver.

Consistent with the effects of a PPARα activator, serum cholesterol and triglycerides were significantly ($p<0.01$) decreased at the mid dose and higher in the F0 and F1 generations, and serum triglycerides were also significantly decreased ($p<0.01$) in F1 males at the low dose. These effects are beneficial.

Absolute and relative kidney weights were significantly ($p<0.01$) increased by >10% in mid-and high-dose F0 males, and relative kidney weight was similarly increased in the F1 males. In the females, increases were small, and statistically significant ($p<0.05$ in the F0 generation and $p<0.01$ in the F1 generation) only at the high dose. There was no kidney histopathology in the F0 generation, but mid-and high-dose F1 males and high-dose F1 females had minimal eosinophilia of proximal tubular epithelial cells. The NOAEL was the low dose for males and the mid dose for females.

Thyroid weight (unclear whether this was absolute or relative) was significantly increased in high-dose F0 females, but not males. In the F1 generation, absolute and relative thyroid weight was significantly ($p<0.01$) increased in males at all doses, but the change was not dose-related; in females, a significant ($p<0.01$) increase was seen only at the high dose.

There was no effect on estrous cycle or on any sperm measure (including sperm motility and sperm count). There was a slight but statistically significant increase in the number of animals with more than 6.5% abnormal sperm at the high dose in the F0 generation, but there was no effect on this parameter in the F1 generation and no effect on the average rate of abnormal sperm in the F0 generation, so this change was considered incidental. There was no effect on male or female reproductive performance, as expressed in terms of the mating or fertility indices. One high-dose male had oligospermia in the left epididymis. There were several statistically significant changes in reproductive organ weights at the high dose, but these were not seen in both generations, or were considered incidental to the decreased body weight. Thus, the high dose of 600 mg/kg-day was a reproductive NOAEL for males and females.

There was no thyroid histopathology in the F0 generation, but thyroid follicular hypertrophy/hyperplasia was observed at the mid- and high-doses in both sexes. In males, there

was no NOAEL and the LOAEL was 40 mg/kg-day, based on increased thyroid weight. In females the LOAEL was 200 mg/kg-day, based on thyroid follicular hypertrophy/hyperplasia. Bhat et al. calculated a $BMDL_{HED}$ of 10 mg/kg-day based on the incidence of thyroid follicular hypertrophy/hyperplasia in F1 males, and used this dose to calculate an RfD. The $BMDL_{HED}$ for this endpoint is similar to the $NOAEL_{HED}$ of about 10 for this endpoint.

Male rats exposed in utero to several phthalates such as DEHP exhibit a spectrum of reproductive/developmental effects related to androgen deficiency, referred to as the "phthalate syndrome." At lower doses, this syndrome is manifested as decreased anogenital distance (AGD) and changes in nipple/areolae retention, while effects at higher doses include malformations of the male reproductive tract, external genitalia (hypospadias), and cryptorchidism (undescended testes). There was no evidence of phthalate syndrome from exposure to DPHP. However, pup body weight was statistically significantly decreased at the high dose in F1 pups (by about 11% on postnatal day 21) and F2 pups (about 8% on postnatal day 21). There was no increase in malformations of variations in either generation. Thus, the high dose is a developmental LOAEL based on decreased pup body weight.

The Union Carbide Corporation (1997) preliminary summary report of the 90-day study of Alpk:APfSD rats (12/sex/dose) fed a diet containing 0, 500, 5000, or 12,000 ppm DPHP for 14 weeks (corresponding to approximately 0, 40, 420, and 1000 mg/kg-day) reported statistically significant ($p<0.01$, 12.5–25%) reductions in sperm velocity indices at the high dose. One velocity index was also significantly ($p<0.05$) reduced at the mid dose, but there was no significant effect on any velocity index in rats treated with the high dose and allowed to recover for 4 weeks. Other indices of sperm viability, such as total sperm, static count, percent motile, motile count, total sperm concentration, and concentration of sperm per gram of tissue, were not significantly affected, and there was no effect on epididymal sperm development. The toxicological significance of the decrease in sperm velocity is unknown, particularly since all other sperm parameters were unaffected, and significant systemic toxicity occurred at the high dose, based on a 23% decrease in body weight compared to controls. Fertility was not assessed.

5.5 Prenatal, Perinatal, and Post-natal Toxicity

In a range-finding developmental toxicity study, pregnant Wistar rats (10/dose) were administered 0, 40, 200, or 1000 mg/kg-day DPHP by gavage in olive oil on gestation days (GD) 6-15 (BASF AG, 1995d, as cited by Bhat et al., 2014 and ECHA, 2018b). The high dose of 1000 mg/kg-day was a maternal and fetal NOAEL.

In the definitive developmental toxicity study (OECD 414), mated female Wistar rats (25/dose) were administered 0, 40, 200, or 1000 mg/kg-day DPHP by gavage in olive oil of GD 6-19 (BASF, 2003, and as cited by Bhat et al., 2014 and ECHA, 2018b). Maternal toxicity occurred at

the high dose, as evidenced by insufficient care of fur, 32% reduced food consumption on GDs 6–10, and 30% reduced corrected body weight gain. Significant loss of body weight (magnitude not specified) occurred on GDs 6–8, consistent with the markedly reduced food consumption during that period at the high dose. Food consumption and body weight gain rebounded after GD 8, but were still decreased by >10% compared to control at the end of the study. Gross necropsy showed that two high-dose females had hydrometra (accumulation of fluid in the uterus). Uterine weight was decreased 19% at the high dose, but the decrease was not statistically significant. Postimplantation loss was significantly increased at the high dose compared with controls (21.3 vs. 6.2%); this increase was attributed primarily to three dams with 100% resorptions. Five of the high-dose females did not become pregnant, but this was not a treatment-related effect, since mating occurred prior to DPHP exposure. Exposure to DPHP did not cause teratogenicity, but fetuses from high-dose females showed a statistically significant increased incidence[3] in soft tissue variations (dilated renal pelvis), which according to the researchers, was just outside the historical control range. In addition, the incidence of the skeletal variations, unossified sternebra, supernumerary rib (without cartilage), and bipartite processus xiphoideus were significantly increased at the high dose, although the total incidence of fetuses with skeletal variations was not increased. The increased fetal variations were considered secondary to maternal toxicity. The maternal LOAEL was 1000 mg/kg-day, based on decreased body weight gain and clinical signs. The developmental LOAEL was 1000 mg/kg-day, based on soft tissue and skeletal variations.

5.6 Genotoxicity

As summarized by Bhat et al. (2014) and ECHA (2018b), DPHP was negative for both gene mutations and chromosome aberrations. DPHP (≥98.7 purity) was negative for gene mutation in the standard plate assay and the pre-incubation assay with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 (BASF AG, 1995c, as cited by Bhat et al., 2014 and ECHA, 2018b). Both studies were conducted in the absence and the presence of S9 activation. It was also negative for gene mutation in mammalian cells, in the Chinese hamster ovary (CHO) cell assay at the HPRT locus (BASF SE, 2010, as cited by Bhat et al., 2014). In Chinese hamster lung fibroblasts (V79 cells), Palatinol® 10-P (98.9% purity) was negative for clastogenicity in the presence and absence of S9 (BASF SE, 2011, as cited by Bhat et al., 2014). No *in vivo* genotoxicity studies with DPHP were located, but ECHA (2018b) noted that the related compound DIDP was negative in the mouse micronucleus assay.

5.7 Mechanistic Studies

The absence of effects associated with phthalate syndrome was supported by the results of Furr et al. (2014). In an attempt to develop a screening assay for effects on fetal testosterone

[3] Bhat et al. (2014) stated that the variations were statistically significant for fetal-based incidences, while ECHA (2018b) stated that the statistical tests for malformations and variations were based on the proportion of affected fetuses per litter. The appropriate approach is evaluation on a per litter basis.

synthesis, Furr et al. (2014) exposed groups of 3 pregnant Sprague Dawley rats to 0 or 750 mg/kg DPHP by oral gavage (vehicle not reported) on GD 14-18. The dams were then sacrificed, and fetal testosterone production was measured. DPHP had no effect on fetal testosterone, while phthalates known to cause phthalate syndrome caused the expected decrease in fetal testosterone. No other mechanistic studies were located.

5.8 Mode of Action

Hepatic Peroxisome Proliferation

Overall, the weight of evidence supports the conclusion that the effects of DPHP on rat liver are occurring via a peroxisome proliferation MOA. Peroxisome proliferation is a well-characterized MOA that applies to many other phthalates, including the related chemical DEHP (reviewed by CPSC, 2014). The key events of this MOA are: 1) activation of PPARα, 2) alteration of cell growth pathways, 3) altered hepatocyte fate, including increased cell proliferation and decreases in apoptosis, and 4) clonal expansion leading to tumors (Klaunig et al., 2003; Felter et al., 2018). Steps two and three of this sequence can manifest as increased relative liver weights due to hepatocellular hypertrophy and proliferation.

DPHP binding to PPARα has not been investigated, but DPHP studies consistently show an increase in PCO activity, a marker for peroxisome proliferation. Hepatocellular hypertrophy and increased liver weight have also been observed in multiple studies, but no chronic studies are available to provide information on whether DPHP causes liver tumors in rodents. The available data are consistent with the conclusion that the key events follow the expected exposure duration-response and dose-response relationships. Peroxisome proliferation is an early event. Increased PCO was observed in rats in a 2-week diet study at the mid dose (10,000 ppm in feed, or about 900 mg/kg-day in male rats and 1000 mg/kg-day in female rats) (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b). It appears that there were no effects on PCO at the low dose (1000 ppm, or about 90 and 100 mg/kg-day in male and female rats, respectively) in this study, and no hypertrophy or significant increase in liver weight at any dose, but the study details were limited. Increased absolute and relative liver weight were also reported in a 5-day inhalation study at the high concentration (1000 mg/m^3 DPHP aerosol), but not at 250 mg/m3. No information was provided on enzyme induction in the inhalation study.

Similarly, in a 13-week study in Wistar rats, PCO and absolute liver weight were increased in females at 2500 ppm in feed (211 mg/kg-day) and there were increases in PCO, liver hypertrophy and absolute liver weight in both sexes at 15,000 ppm in feed (1187 mg/kg-day for males and 1344 mg/kg-day for females). Results from the other subchronic study, conducted in Alpk:APfSD rats (Union Carbide Corporation, 1997, 1998) were also consistent with a peroxisome proliferation MOA, although documentation was less complete. Peroxisome enzyme levels and liver weight were increased in all treatment groups (500, 5000, or 12,000 ppm DPHP in feed, corresponding to about 40, 420, and 1000 mg DPHP/kg-day), and PCO was increased at the mid and high doses. It is not clear why liver weight was reported as being increased at a lower dose than the PCO increase, but “peroxisome enzymes” were increased at the low dose,

and so this result does not appear to violate the expected dose-response pattern. It is possible that PCO was increased but the increase was not statistically significant, and so was not reported in the available summary. Decreases in plasma cholesterol and triglyceride were also observed in the second subchronic study, and are consistent with peroxisome proliferation, although the affected doses were not reported.

Thus, although there are some data gaps for DPHP, the overall database, including information on other phthalates (reviewed by CPSC, 2014), supports the conclusion that the liver effects of DPHP can be attributed to a peroxisome proliferation MOA. Activation of CAR may also play a role, based on analogy to other phthalates (Bhat et al., 2014), but no specific data are available about the effect of DPHP on CAR. No chronic studies are available for DPHP, and it is not known whether it causes liver tumors in rodents. However, both liver tumors occurring via either the peroxisome proliferation or CAR MOA are considered not likely to be relevant to humans (Klaunig et al., 2003; Felter et al., 2018).

Disruption of Hypothalamus-Pituitary-Thyroid (HPT) Axis

Bhat et al. (2014) speculated that pituitary gland changes (increased basophilic cells) in the subchronic Wistar rat study (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b) and thyroid follicular hypertrophy/hyperplasia seen in that study and the two-generation study (BASF AG, 2009, as cited by Bhat et al., 2014 and ECHA, 2018b) may have been secondary to induction of liver metabolic enzymes (e.g., UGT) by PPARα or CAR. According to this MOA, increased hepatic clearance of the thyroid hormones T3 and T4 leads to a compensatory increase in TSH, followed by thyroid hypertrophy and ultimately thyroid hyperplasia and tumors in rodents (Capen, 1997). This MOA is also considered not relevant to humans for tumorigenesis, but it is relevant for neurodevelopmental effects (Dellarco et al., 2006).

Although there is support for DPHP affecting the HPT axis, based on the changes in the pituitary gland and thyroid noted in the previous paragraph, the data are insufficient to support any specific MOA. No data are available for the effect of DPHP on UGT activity, or on levels of TSH, T3, or T4. Similarly, the data on other phthalates are insufficient to support any specific MOA, although other phthalates, such as DEHP and di-octyl phthalate, have also been shown to cause thyroid effects in rats (reviewed by Bhat et al., 2014) and are suspected of affecting thyroid hormone levels in humans (Kim et al., 2018). More recently, Sun et al. (2018) found that DEHP increased levels of thyroid releasing hormone (TRH) and decreased the levels of T3 and T4 in adolescent rats. TSH levels were not significantly changed, but visual inspection of the graphical data suggests a similar trend for TSH as seen for the other hormones, even though it was not statistically significant.

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

Only one repeated-exposure inhalation study is available. In that study, male Wistar rats were exposed to a DPHP aerosol for 6 hours/day for 5 consecutive days. The NOAEC was 50 mg/m^3 and the LOAEC was 250 mg/m^3 for effects on the respiratory tract, including increased lung weight, inflammation, histocytosis, and hypertrophy of the bronchioles. Hepatocellular

hypertrophy and increased liver weight were also seen at 1000 mg/m^3, and were considered adaptive.

The liver is a primary target in many of the repeated dose studies, although all of the observed changes were adaptive, rather than adverse, and downstream events (liver hypertrophy, and tumors, if they occur) are not considered relevant to humans. In a 2-week study (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b), increased PCO activity was seen at about 1000 mg/kg-day and higher in male and female Wistar rats[4]. Similarly, in a 13-week study in Wistar rats (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b), PCO and absolute liver weight were increased in females at 211 mg/kg-day and higher and in males at 1187 mg/kg-day and higher. In a subchronic study in Alpk:APfSD rats that was not well documented, increased peroxisome enzyme levels and increased liver weights were seen at all doses, including the low dose of 40 mg/kg-day (Union Carbide Corporation, 1997, 1998, and as cited by ECHA, 2018b). It is not clear why the apparent effect level was lower in the latter study, although it could be due to either strain differences or differences in the definition of an effect. In the two-generation study in Wistar rats (BASF AG, 2009, as cited by Bhat et al., 2014 and ECHA, 2018b), increased absolute and relative liver weights were seen at 200 mg/kg-day, but not at 40 mg/kg-day.

As was seen for the liver, the Alpk:APfSD rats may have been more sensitive than Wistar rats to the effects of DPHP on body weight. Biologically significant decreases in body weight relative to controls were seen in the subchronic study with Alpk:APfSD rats at 1000 mg/kg-day (Union Carbide Corporation, 1997, 1998; and as cited by ECHA, 2018b), while in the subchronic Wistar study, the decrease in body weight relative to controls at a similar dose (somewhat above 1000 mg/kg-day) were <10% (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b). However, decreased food consumption (degree of change not reported) was noted in the former study, but not the latter study. Decreased maternal body weight gain was also seen in a developmental toxicity study in Wistar rats at 1000 mg/kg-day (BASF, 2003, and as cited by Bhat et al., 2014 and ECHA, 2018b), and decreased parental body weight compared to controls occurred in the two-generation study in Wistar rats at 600 mg/kg-day (BASF AG, 2009, as cited by Bhat et al., 2014 and ECHA, 2018b).

The data suggest that the thyroid is also a target for effects of DPHP. Thyroid hypertrophy was seen in male and female Wistar rats exposed for 13 weeks to about 200 mg/kg-day in feed (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b). Increased basophilic cells in the anterior part of the pituitary gland were also seen in the Wistar rat study at about 200 mg/kg-day in males, but not in females even at the high dose of 1344 mg/kg-day (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b). The observation of effects in both the thyroid and this portion of the pituitary suggests that DPHP may affect the HPT axis, but it is not clear why the pituitary was affected in males but not females. No effect on the thyroid was reported in Alpk:APfSD rats exposed subchronically to doses up to about 1000 mg/kg-day (Union Carbide Corporation, 1997, 1998; and as cited by ECHA, 2018b).

[4] Note that levels for all effects are reported here, while Table 5 lists adverse effect levels.

The adrenal may also be a target, although different effects were seen in the two subchronic studies. In the Wistar rat study, decreased absolute adrenal weight was seen in males at 1187 mg/kg-day, but not in females at a similar dose (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b). In the Alpk:APfSD rat study, vacuolization of the *zona glomerulosa* was seen in both sexes at the lowest dose tested, 40 mg/kg-day.

Significant increases in absolute and relative kidney weight (accompanied by decreased body weight) were seen in the two generation study at 200 mg/kg-day in males and 600 mg/kg-day in females (BASF AG, 2009, as cited by Bhat et al., 2014 and ECHA, 2018b). Significantly increased relative kidney weight and decreased body weight were also observed in the subchronic Wistar rat study at about 1000 mg/kg-day (BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018b), but not in the subchronic study in Alpk:APfSD rats. Minimal eosinophilia of proximal tubular epithelial cells in the F1 generation was also seen in the two generation study at the same dose as that causing the increased kidney weight.

Mild developmental toxicity was seen with DPHP. Soft tissue and skeletal variations were reported in the pups of dams treated by gavage with 1000 mg/kg-day during GD 6-19, a dose that also caused significant postimplantation loss and maternal toxicity in the form of decreased body weight and insufficient care of fur (BASF, 2003, and as cited by Bhat et al., 2014 and ECHA, 2018b). No effect on fetal testosterone was seen in the offspring of Sprague-Dawley rat dams treated with 750 mg/kg-day on GD 14-18, indicating that DPHP does not cause phthalate syndrome at doses up to 750 mg/kg-day. In a two-generation study with Wistar rats, decreased pup body weight was seen at 600 mg/kg-day in both the F1 and F2 generations (BASF AG, 2009, as cited by Bhat et al., 2014 and ECHA, 2018b).

There were no effects on reproductive indices or on reproductive organ pathology in a two-generation reproductive toxicity study with Wistar rats tested up to 600 mg/kg-day. Decreased sperm velocity indices were reported in Alpk:APfSD rats treated with 1000 mg/kg-day for 13 weeks (Union Carbide Corporation, 1997, 1998; and as cited by ECHA, 2018b), but the toxicological significance of this finding is uncertain, in the absence of effects on other sperm indices.

The data indicate that DPHP is not genotoxic, based on negative results for gene mutation in bacteria (BASF AG, 1995c, as cited by Bhat et al., 2014 and ECHA, 2018b) and in CHO cells (BASF SE, 2010, as cited by Bhat et al., 2014). DPHP was also negative for clastogenicity in Chinese hamster lung fibroblasts (BASF SE, 2011, as cited by Bhat et al., 2014).

The data are insufficient to evaluate the carcinogenic potential of DPHP.

Adverse effect levels of DPHP (or effect levels where the adversity of the change is ambiguous) are summarized in Table 5.

5.10 Uncertainties and Data Gaps

Several uncertainties of varying importance were identified in this assessment.

Database:

The overall database on DPHP is fairly complete, including subchronic studies, a developmental toxicity study, and a two-generation reproductive toxicity study. However, although these key study types were conducted according to test guidelines, all of the repeated-dose studies were conducted in rats and only summaries in secondary sources are available. Only limited inhalation data are available, and the only dermal data were irritation and sensitization studies. No carcinogenicity data are available.

Key data gaps are the lack of data from a second species for repeated dose toxicity and developmental toxicity. In particular, the observations of thyroid effects suggests the potential for neurodevelopmental effects secondary to thyroid hormone disruption. ECHA (2014) also recommended that more detailed information be obtained about potential adverse effects on the pituitary and thyroid glands.

Hazard:

Thyroid and pituitary: The MOA for the observed effects is unknown, making it difficult to consider the human relevance and implications of the observed changes. In particular, information on changes in thyroid hormone levels would be useful to aid in clarifying the effect, although inhibitor studies would probably be needed to determine the MOA.

Reproductive: Although it is clear that DPHP does not cause phthalate syndrome, the significance of the decreased sperm velocity is unclear, particularly in the absence of effects on other sperm parameters.

Hematology: The biological significance of the statistically significant change in several hematology parameters in the subchronic Alpk:APfSD rat study is unclear in the absence of information on the magnitude of the changes.

Table 5. Summary of NOAELs/LOAELs Identified for DPHP by Organ System

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified	Toxicological Basis	Comments
Inhalation					
Wistar rat (M) 10/group Anonymous, 2013, as cited by ECHA, 2018	0, 50, 250, or 1000 mg/m^3 6 hours/day 5 consecutive days.	Respiratory tract	NOAEC = 50 mg/m^3 LOAEC = 250 mg/m^3	Respiratory tract inflammation, hypertrophy and hyperplasia	
		Liver	NOAEC = 1000 mg/m^3	Liver weight increased by 30%; hepatocellular hypertrophy.	Changes considered adaptive
Oral					
Wistar rat (M and F) (#/dose not specified) BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018	2 weeks Diet 0, 1000, 10,000, or 20,000 ppm M: 0, 92, 920, 1840 mg/kg-day F: 0, 102, 1020, 2040 mg/kg-day	Liver	NOEL = 92 (M) LOEL = 920 (M) NOEL = 102 (F) LOEL = 1020 (F)	Increased PCO activity	Limited information available and it is unclear whether other endpoints were evaluated. Dose conversion for middle dose from Bhat et al. (2014); other doses calculated by proportionality PCO is a marker for peroxisome proliferation.
Wistar rat (M and F) (10/sex/dose)	13 weeks	Liver	NOAEL = 1187 (M) NOAEL = 1344 (F)	Increased absolute liver weight and hypertrophy	Absolute liver weight increased by >50%, but changes considered adaptive and not likely to be adverse

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified	Toxicological Basis	Comments
BASF AG, 1995b, as cited by Bhat et al., 2014 and ECHA, 2018	Diet (OECD TG 408) 0, 500, 2500 or 15,000 ppm M: 0, 36, 181 or 1187 mg/kg-day F: 0, 42, 211 or 1344 mg/kg-day Human equivalent doses (HEDs): M: 0, 10, 51, and 331 mg/kg-day F: 0, 11, 53, and 328 mg/kg-day (Bhat et al., 2014)	Adrenal	NOAEL = 181 (M) LOAEL = 1187 (M) NOAEL = 1344 (F)	Decreased absolute adrenal weight	Not accompanied by any histopathology, but decrease is larger than the corresponding decrease in body weight
		Kidney	NOAEL = 1187 (M) NOAEL = 1344 (F)	Increased relative kidney weight	Potentially relevant to humans, but likely related to decreased body weight and likely not adverse.
		Thyroid	NOAEL = 36 (M) LOAEL = 181 (M) NOAEL = 42 (F) LOAEL = 211 (F)	Thyroid hypertrophy	Potentially secondary to increased thyroid hormone clearance and thus potentially not relevant to humans, but MOA has not been demonstrated. Thyroid weight and thyroid hormone levels were not measured.
		Pituitary	NOAEL: 36 (M) LOAEL: 181 (M) NOAEL = 1344 (F) LOAEL = N/A (F)	Increased basophilic cells in the anterior part of the pituitary gland	Potentially secondary to increased thyroid hormone clearance and thus potentially not relevant to humans, but MOA has not been demonstrated.
Alpk:APfSD rats (M and F) (12/sex/dose)	14 weeks Diet	Body weight	NOAEL = 420 LOAEL = 1000	Decreased body weight gain	Decreases of 23% and 19% in males and females, respectively
		Hematology	NOEL = 40 (M) LOEL = 420 (M)	Decreased red blood cell count, hemoglobin, and	No information on the magnitude of the change available, so the adverse effect level cannot be identified

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified	Toxicological Basis	Comments
Union Carbide Corporation (1997, 1998) and as cited by ECHA (2018)	0, 500, 5000, 12,000 ppm Approximately 0, 40, 420, 1000 mg/kg-day		NOEL = 420 (F) LOEL = 1000 (F)	hematocrit; increased platelet counts	
		Liver	NOAEL = 1000	Increased peroxisome enzymes, liver weight seen at all doses	Changes were adaptive and likely secondary to peroxisome proliferation
		Adrenal gland	NOAEL = N/A LOAEL = 40 (M, F)	Vacuolization of the *zona glomerulosa*	Hypothesized to be secondary to peroxisome proliferation, and thus not relevant to humans, but support is insufficient.
		Reproductive	NOEL = 420 (M) LOEL = 1000 (M)	Decreased sperm velocity indices	Toxicological significance is uncertain in light of absence of effects on other sperm indices, and in light of the 23% decrease in body weight. Fertility was not assessed. Reproductive indices were not evaluated in females
Wistar rat (F) 10/dose BASF AG. 1995d, as cited by Bhat et al., 2014 and ECHA, 2018	GD 6-15 Gavage in olive oil 0, 40, 200, or 1000 mg/kg-day	Maternal	NOAEL = 1000	No effects	Range-finding study
		Developmental	NOAEL = 1000	No effects	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified	Toxicological Basis	Comments
Wistar rat (F) 25/dose BASF, 2003, and as cited by Bhat et al., 2014 and ECHA, 2018	GD 6-19 OECD 414 Gavage in olive oil 0, 40, 200, or 1000 mg/kg-day	Maternal	NOAEL = 200 LOAEL = 1000	Insufficient care of fur, decreased body weight and body weight gain, decreased food consumption	Postimplantation loss significantly increased at high dose, primarily due to 3 dams with 100% resorptions.
		Developmental	NOAEL = 200 LOAEL = 1000	Soft tissue variations (dilated renal pelvis), and skeletal variations unossified sternebra, supernumerary rib (without cartilage), and bipartite processus xiphoideus	Variations were likely secondary to maternal toxicity.
Sprague-Dawley rat (F) 3/dose Furr et al. (2014)	GD 14-18 Gavage 0 or 750 mg/kg	Developmental – fetal testosterone	NOAEL = 750	No effect	Study investigates the development of a screening assay. Phthalates known to cause phthalate syndrome caused the expected decrease in fetal testosterone
Wistar rat (M, F) 25/sex/dose BASF AG, 2009, as cited by Bhat et al., 2014	2-generations OECD 416 Diet Target doses of 0, 40, 200, or 600 mg/kg-day, dietary	Body weight	NOAEL = 200 LOAEL = 600	Statistically significant decrease in body weights by >10%	Similar responses in the F0 and F1 generations
		Kidney	NOAEL = 40 (M) LOAEL = 200 (M) NOAEL = 200 (F) LOAEL = 600 (F)	Statistically significant increases in organ weight ≥10%. Minimal eosinophilia of proximal tubular epithelial cells in the F1 generation	Similar organ weight responses in the F0 and F1 generations, but histopathology seen only in the F1 generation

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified	Toxicological Basis	Comments
and ECHA, 2018	concentration adjusted weekly to maintain target dose	Liver	NOAEL = 600	Increased absolute and relative liver weight, hypertrophy, increased ALP	Changes in liver weight and hypertrophy were adaptive and likely secondary to peroxisome proliferation. Increased ALP not supported by increased transaminases
		Thyroid	NOAEL = N/A (M) LOAEL = 40 (M) NOAEL = 40 (F) LOAEL = 200 (F)	Increased thyroid weight in males. Thyroid follicular hypertrophy/hyperplasia in both sexes at 200 and above	Potentially secondary to increased thyroid hormone clearance and thus potentially not relevant to humans, but MOA has not been demonstrated.
		Developmental	NOAEL = 200 (F1 and F2) LOAEL = 600 (F1 and F2)	Decreased pup body weight	Decrease by about 11% in F1 pups and about 8% in F2 pups
		Reproductive	NOAEL = 600 mg/kg-day (M, F)	No effect	Several incidental statistically significant changes in reproductive organ weight

6 Exposure

The use of DPHP in consumer products was described in Section 3 of this report. Consumers are exposed indirectly to DPHP through products and materials containing the phthalate ester, while workers may be exposed from manufacturing activities. The majority of HMWPEs in the environment likely come from slow release from polymers (e.g., PVC) containing the phthalates due to weathering and product use (OECD, 2004).

Because DPHP is not chemically bound to PVC, it may be released from end-products made of PVC over time through evaporation, leaching, or abrasion, resulting in possible skin and inhalation exposure, ingestion from mouthing of products, dermal contact with products and dust, and from hand-to-mouth behaviors leading to ingestion. No information could be found on leaching or migration of DPHP from polymer resins in the context of consumer exposure evaluation.

ECHA (2018a) reported that DPHP is likely to be released at low rates from materials such as metal, and wooden and plastic construction and building materials used outdoors. Indoors, materials such as flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, and electronic equipment are likely to release DPHP at low rates. Products using DPHP as a binding agent (e.g., in paints, coatings, and adhesives) are also sources of release (ECHA, 2018a).

A closed system is used for commercial manufacturing of DPHP, wherein phthalic anhydride is catalytically esterified with isomeric decyl alcohols (primarily 2-propyl heptanol) and the unreacted alcohols are recovered and reused (CPSC, 2014). Occupational exposure may occur during production, packaging, or cleaning of equipment (NICNAS, 2003), with primary potential exposure via the dermal route and the potential for aerosol exposure with some applications (OECD, 2004).

There are several studies that measured DPHP concentrations in various environmental media and calculated daily DPHP intakes, and this text focused on these studies, because they assess the most relevant pathways and exposure sources. In addition, a number of studies measured urinary metabolites and a few studies estimate exposure based on the biomonitoring data. The biomonitoring data are presented first, followed by the exposure studies.

6.1Biomonitoring

Distinguishing between metabolites of DPHP and DIDP has not been possible until fairly recently when Gries and colleagues developed a new analytical method, resulting in biomonitoring data reporting exposure to the two phthalates combined. Gries et al. (2012) developed a gas chromatography high resolution mass spectrometry (GC–HRMS) analytical method that is reliably specific and sensitive in distinguishing between DPHP metabolites and DIDP metabolites at background levels in urine. Limits of detection (LODs) and corresponding limits of quantification (LOQs) are 0.05 µg/L (0.15 µg/L) for cx-MPHxP, 0.1 µg/L (0.3 µg/L) for OH-MPHP, and 0.08 µg/L (0.25 µg/L) for oxo-MPHP. This text focuses on the more recent studies that utilized the

newer method to measure DPHP-specific metabolites in urine, and thus are not confounded by DIDP exposure.

Gries et al. (2012) used their method to assess DPHP metabolites from 40 random spot urine samples from adults who were not occupationally exposed. The maximum urinary concentrations were 0.93 µg/L oxo-MPHP and 0.51 µg/L for OH-MPHP. Concentrations of cx-DPHP were all below the LOQ.

Leng and Gries (2017) reported on biomonitoring of urine from 51 German volunteers using the GC-HRMS method. Of the 51 samples, 20 had concentrations greater than the limit of quantification (LOQ) for OH-MPHP, and 17 had concentrations greater than the LOQ for oxo-MPHP. They reported mean concentrations for the metabolites of 0.507 µg/L (range 0.15[5] µg/L - 3.81 µg/L) for OH-MPHP and 0.404 µg/L (range 0.125 µg/L – 3.27 µg/L) for oxo-MPHP. In contrast, none of the samples had concentrations of cx-MPHP that exceeded the LOQ.

To investigate how increased usage of DPHP over time is reflected in urine samples, Schutze et al. (2015) analyzed 24-hour voids collected in Germany over a 14-year period (1999-2012). Sixty samples (30 male and 30 female, 20-30 years old) collected in each of five years (1999, 2003, 2006, 2009, and 2012) were analyzed for the three secondary oxidized DPHP metabolites using the GC-HRMS method of Gries et al. (2012). None were detected in samples from 1999, 2003, or 2006. Oxo-MPHP was detected in samples collected in 2009 (3.3% detection frequency) and 2012 (21.7% detection frequency), with maximum concentrations of 0.96 µg/L (2009) and 0.65 µg/L (2012). OH-MPHP was detected in 3.3% of the samples in 2009 and again in 2012, with maximum concentrations of 0.64 µg/L (2009) and 0.36 µg/L (2012). The cx-MPHP metabolite was not detected in any samples. The authors concluded that the oxo-MPHP metabolite levels indicate recent measurable exposure to DPHP in the German population, a finding that they considered to be a logical consequence of increased use of DPHP as a substitute phthalate.

Table 6 summarizes the results of these three studies that used the GC-HRMS method of Gries et al. (2012), which can reliably distinguish between DPHP and DIDP exposure.

[5] For both metabolites, the lower end of the range is the LOQ/2 for that compound.

Table 6. Results of biomonitoring studies measuring urine metabolites using the GC-HRMS method (Gries et al., 2012)

Study	Details	Oxo-MPHP	OH-MPHP	cx-MPHP
Gries et al., 2012	Random spot samples, 40 adults not exposed occupationally	Range[a]: 0.25 µg/L – 0.93 µg/L Frequency > LOD: 38%	Range[a]: 0.3 µg/L – 0.51 µg/L Frequency > LOD: 8%	All samples < 0.15 µg/L (LOQ) and <LOD
Leng and Gries, 2017	51 German volunteers; no additional details provided	Maximum: 3.27 µg/L Mean: 0.404 µg/L Range[b]: 0.125 µg/L – 3.27 µg/L Frequency > LOQ: 33%	Maximum: 3.81 µg/L Mean: 0.507 µg/L Range[b]: 0.15 µg/L – 3.81 µg/L Frequency > LOQ: 39%	All samples < 0.075 µg/L (LOQ/2)
Schutze et al., 2015	24-hour voids; 30 males, 30 females ages 20-30 years; collected in each of 5 years (1999, 2003, 2006, 2009, 2012) in Germany			
	1999 – 2006	Not detected	Not detected	Not detected
	2009	Maximum: 0.96 µg/L Median: < LOQ (0.25 µg/L) Range[a]: 0.25 µg/L – 0.96 µg/L Frequency > LOQ: 3.3%	Maximum: 0.64 µg/L Median: < LOQ (0.3 µg/L) Range[a]: 0.3 µg/L – 0.64 µg/L Frequency > LOQ: 3.3%	Not detected (LOQ: 0.15 µg/L
	2012	Maximum: 0.65 µg/L Median: < LOQ (0.25 µg/L) Range[a]: 0.25 µg/L – 0.65 µg/L Frequency > LOQ: 21.7 %	Maximum: 0.36 µg/L Median: < LOQ (0.3 µg/L) Range[a]: 0.3 µg/L – 0.36 µg/L Frequency > LOQ: 3.3%	Not detected (LOQ: 0.15 µg/L

[a] Lower end of range is the LOQ for that metabolite.
[b] Lower end of range reported as LOQ/2 for that metabolite.

Alves et al. (2017) measured DPHP metabolites that they had identified in vitro in the fingernails (MPHP and OH-MPHP; n=59) and in morning urine (MPHP, OH-MPHP, and oxo-MPHP; n=61) of Norwegian volunteers living in greater Oslo. None of these metabolites were detected in any sample, but the limits of detection were not reported. The authors noted that quantification was

difficult, due to the absence of commercial standards for the metabolites and that sensitive extraction and analytical tools are needed to measure oxidative metabolites in urine. The authors also noted that low detection frequencies in their study and others (e.g., Gries et al. 2012; Leng et al., 2014) indicates a low ability to identify DPHP exposure from its metabolites and possible low rates of formation in vivo as suggested by their in vitro data (Alves et al., 2017).

Other studies measured metabolites using methods that cannot reliably distinguish between DPHP and DIDP exposure. For example, Larsson et al. (2017) obtained urine samples (first morning void) from 113 preschool children from 28 preschools in Sweden. The metabolites they measured (monohydroxyisodecyl phthalate, MHiDP, and mono(hydroxyisononyl) phthalate, MCiNP) are not specific to DPHP.

Several studies reported measurement of metabolites in pregnant women and their children, but these studies did not use methods that could reliability differentiate between metabolites of DPHP and DiDP. These studies are described here because they were conducted with populations of particular interest, although the contribution of DPHP exposure to these measurements is not known.

Metabolites were measured in urine of 104 mother-child pairs (mean age of mothers was 39.2 years and children was 6.8 years; children were born between 2000 and 2002) from the Duisburg birth cohort study in Germany (Kasper-Sonnenbe et al., 2012). Measured metabolites for DIDP and DPHP were reported together. The metabolites 6-OH-mono-propyl-heptyl phthalate (OH-MiDP), 6-oxo-mono-propyl-heptyl phthalate (oxo-MiDP), and mono-(2,7-methyl-7-carboxy-heptyl) phthalate (cx-MiDP) were found above the LOQ (0.2 µg/L) in 95% and greater of the children's urine. The geometric mean concentrations for children were: 2.1 µg/L (range <LOQ - 63.8 µg/L) for OH-MiDP; 0.6 µg/L (range <LOQ – 19.2 µg/L) for oxo-MiDP; and 1.3 µg/L (range <LOQ – 45.3 µg/L) for cx-MiDP. OH-MiDP, oxo-MiDP, and cx-MiDP were found above the LOQ in 89% or greater of the mothers' urine. The geometric mean concentrations for mothers were 1.7 µg/L (range: <LOQ - 34.0 µg/L) for OH-MiDP; 0.4 µg/L (range: <LOQ – 15.4 µg/L) for oxo-MiDP; and 0.6 µg/L (range: <LOQ – 16.3 µg/L) for cx-MiDP. Both mothers and children showed higher excretion levels for the secondary metabolites than the simple monoesters, with the children's levels greater than those of the mothers. Concentrations were correlated between the mothers and children, which the authors considered to be due to their shared environmental exposure.

In another study with pregnant women, Shu et al. (2018) studied temporal trends in phthalate metabolites. MHiDP and MCiNP were measured in first trimester urine samples of 1651 pregnant women in the Swedish SELMA study (LOD for these two metabolites was 0.031 µg/L). DiDP and DPHP metabolites were reported as a sum in this study due to the difficulty of differentiating between them. The authors reported that the combined metabolite levels showed a statistically significant upward trend in concentration over the course of the sampling period (2007-2010), while DEHP concentrations, in contrast showed a statistically significant downward trend.

As described in a publication by Apel et al. (2017), the German Human Biomonitoring Commission (HBM Commission) derived a human biomonitoring value (HBM-1) for the combined levels of the DPHP urinary metabolites, OH-MPHP and oxo-MPHP. The HBM-1 represents the

concentration below which, "there is no risk for adverse health effects and, consequently, no need for action" (UBA, 2018). The HBM-1 is based upon a Tolerable Daily Intake (TDI) of 0.2 mg/kg-day, which was derived from the NOAEL of 39 mg/kg-day (rounded to 40 mg/kg-day) based on effects in the thyroid and the pituitary gland in a subchronic rat study by BASF (1995b). A total assessment factor of 200 was used (2 for extrapolation from subchronic to chronic duration, 10 for intraspecies variability, and 10 for interspecies variability). The TDI was then used to derive the HBM based on an average ratio of the molecular weight of the metabolites to that of DPHP of 0.72, urinary excretion factor (fue(48 hours)) of 0.24 for the two metabolites combined (Leng et al., 2014), volume of urine for children of 0.03 L/kg-day, and volume of urine for adults of 0.02 L/kg-day. Based on these parameters, the HBM Commission calculated HBM-I values in urine for the combined metabolites (after rounding) of 1 mg/L for children and 1.5 mg/L for adults.

6.2 Exposure and uptake studies

A number of studies calculated daily DPHP intakes based upon biomonitoring data and/or exposure measurements and compared these to various safe doses. As noted above, most of the biomonitoring studies measured metabolites that are not specific to DPHP (e.g., they are common to DiDP and DPHP).

Schutze et al. (2015) investigated how increased usage of DPHP in Germany is reflected in urine samples (collected from adults from 1999 and 2012 - see biomonitoring discussion above for more details). This was the only study located that calculated exposure intakes using metabolites specific to DPHP. The authors calculated daily DPHP intakes using the sum of the OH-MPHP, oxo-MPHP and cx-MPHP metabolite concentrations above the LOQ (total = 1.6 µg/L). The highest DPHP intake calculated was 0.32 µg/kg-day for one individual in 2009. The authors noted that this value is well below the RfD calculated by Bhat et al. (2014) of 0.1 mg/kg-day. Schutze et al. (2015) concluded that DPHP has reached the general German population but exposure is lower than other HMWPEs and some of their substitutes. They noted that production or consumption volume is not necessarily a good predictor of body burden, because different phthalates and substitutes are used in different types of products, with differences in proximity to the consumer contributing to exposure. For example, DINCH®[6] is used in food packaging, toys and medical devices, while DPHP is used in carpet backing, cables, roofing membranes and car interiors.

The CHAP on Phthalates and Phthalate Alternatives (CPSC, 2014) used human biomonitoring data on prenatal and postnatal measurements in women and measurements in infants from NHANES (2005-2006 data) and the Study for Future Families (Sathyanarayana et al., 2008a; 2008b) to estimate daily intake levels, calculate cumulative exposure, and compare with health benchmarks to evaluate risk using hazard indices. However, CPSC (2014) presented DIDP/DPHP data together because of the lack of methods to differentiate DPHP metabolites from DIDP metabolites at the time and so no further details are included here. CPSC (2014) did note that CPSC had recently detected DPHP in some childrens' toys; additional details were not provided.

[6] DINCH® is a registered trademark of BASF and the common abbreviation for 1,2-Cyclohexanedicarboxylic acid, dinonyl ester, branched and linear.

Due to concern about the potential for children's exposure to phthalate esters, some studies have evaluated DPHP in toys. McCombie et al. (2017) tested 118 samples from 88 toys taken from the Swiss market in 2015 for compliance with the 0.1% restriction for phthalate content. DPHP was found in four of the samples in amounts over 0.1% (range 0.6% – 27.8% by weight), but the authors did not calculate exposure. The German BfR (2011) reported that DPHP has been detected in four children's toys with concentrations ranging from 10.1% to 48.2% by weight. They estimated exposure from these toys to be up to 135 µg/kg-day and compared this daily intake to a safe intake dose of 40 µg/kg-day (unspecified NOAEL divided by safety factor of 100 and an additional factor of 10 due to children being exposed to DPHP through other routes and sources). The BfR concluded that it is necessary to reduce levels of DPHP in toys. The intake calculated here based upon toy exposure alone is much higher than what has been reported by others looking at different and sometimes multiple routes of exposure (but not toys specifically). The report is in German and no further details were available in the English abstract.

Giovanoulis et al. (2018) performed a multi-pathway human exposure assessment of a number of phthalate esters and DINCH®, and estimated intake for adults living in Norway. For DPHP, the authors estimated daily intake from measurements in various environmental media. They did not, however, estimate intake based on biomonitoring data, because of the low detection frequency of the DPHP metabolite MPHP in all the urine samples; other metabolites were not investigated. Because this is a recent study that conducted a multi-pathway evaluation of total exposure, it is described in some detail. Sixty-one adults aged 20-66 (16 males and 45 females) participated during 2013 to 2014. Dietary, biological, and environmental samples were collected during a 24-hour period in each person's household (indoor and personal air samples, floor dust, duplicate diet food samples, vacuum cleaner bag dust, and hand wipes). Questionnaires were used to gather information about personal and lifestyle characteristics and the home environment. Inhalation exposure (both gaseous and particulate phase) was estimated using the stationary indoor air samples. Dietary intake was based on measured food concentrations. Dust ingestion was based on the vacuum cleaner bag dust. Dermal uptake was estimated using hand wipe samples as well as exposure via dust and air. Concentrations of DPHP in personal care products application rates were obtained from other studies

The detection frequency for food (duplicate diet) was 72.1%; floor dust, 96.7%; vacuum cleaner bag dust, 98.2%; and handwipes, 100%. The detection frequency in air was much lower (stationary air, 4.9% and personal air, 33.3%). The authors provided medians and 95th percentiles for the concentration in each medium. The 95th% concentrations for each of the media were as follows: diet, 12.3 ng/g; floor dust, 126.2 µg/g; vacuum cleaner bag dust, 18.8 µg/g; handwipes, 25.9 $\mu g/m^2$; stationary air, < LOD (5 ng/m^3); and personal air, 55.6 ng/m^3. DPHP showed a positive association between floor dust and dust from vacuum cleaner bags.

The authors calculated daily intakes for each exposure route and pathway; see Table 7. Dietary intake was the primary source of DPHP exposure (~>85%), with a very small amount from inhalation, and the remainder from dust. They estimated a median daily intake from all sources of

0.04 µg/kg-day. Comparing this to the TDI of 200 µg/kg-day (UBA, 2015) results in a very low hazard quotient (HQ) of 0.00021 (95^{th} percentile HQ = 0.0012).

Table 7. Calculated DPHP daily intakes (geometric mean [range] in ng/kg/day) from Giovanoulis et al. (2018). Adapted from Table SI-2 of Giovanoulis et al. (2018).

Pathway	DPHP Daily Intake (ng/kg-day) Median (range)
Inhalation	0.51 (0.35-1.52)
Dust ingestion	3.62 (0.12-29.1)
Dietary intake	27.5 (0.6-2738)
Dermal uptake via hand wipes	0.004 (3.4×10^{-4}-0.04)
Dermal uptake via dust	2×10^{-4} (8.2×10^{-6}-0.002)
Dermal uptake via air	7.2×10^{-5} (5.1×10^{-5}-2.1×10^{-4})
Dermal uptake via personal care products	0.03 (0.002-0.08)
Total	35.8 (2.5-2276) rounded to 0.04 µg/kg-day

Larsson et al. (2017) investigated levels of DPHP in dust collected from 100 Swedish preschools in 2015 in order to identify products and characteristics of the preschools that are important to exposure. Settled dust was collected from elevated surfaces with 100% detection rate for DPHP. Concentrations ranged from 0.15 µg/g – 2600 µg/g (geometric mean = 8.2 µg/g and 95th% = 42 µg/g). They estimated a geometric mean daily DPHP intake from dust of 0.01 µg/kg-day (95th% = 0.06 µg/kg-day). The authors also analyzed urine samples from children in 28 of the preschools as well as spot urine samples from other Swedish children collected between 1998 and 2000 (BAMSE birth cohort). However, the metabolites measured in this study (MHiDP and MCiNP) are reported for DiDP/DPHP combined, and so these data are not reported here.

Table 8 summarizes DPHP intake estimates from studies that differentiated between DPHP and DIDP exposure and metabolites.

Table 8. Daily DPHP intake estimates from four studies.

Study	Details	Estimates of Daily Uptake µg/kg-day
Larsson et al. (2017)	Intake calculated from dust concentrations for children exposed to dust in preschool environment	Geometric mean: 0.01, child 95th%: 0.06, child
German BfR (2011)	Calculated for child exposure to toy containing 48.2% DPHP by weight, no further details available	Highest: 135, child Central tendency not available
Schutze et al. (2015)	Calculated based on sum of OH-, oxo- and cx-MPHP metabolites from general adult population of adults, collected in 2009	Highest: 0.32, adult Central tendency not provided
Giovanoulis et al. (2018)	Multi-pathway assessment (adults) including exposure to air, diet, dust, and dermal exposure measured with handwipes	Median: 0.04, adult Highest: 2.276, adult Range: 0.0025 – 2.276, adult

7 Discussion

7.1 Toxicity Under FHSA

Animal data support the conclusion that **DPHP does not fit the designation of acutely toxic under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A))** following single oral exposures. The acute LD_{50} value for DPHP in rats was >5,000 mg/kg (Nuodex, Inc., 1979a, as cited by Versar, 2011). Similarly, a dermal LD_{50} >2,000 mg/kg was reported in rabbits (Nuodex, Inc., 1979b, as cited by Versar, 2011). No 4-hours inhalation study with DPHP is available, but a 1-hour study in rats exposed to aerosolized DPHP (particle diameter = 3–5 microns) suggests a 1-hour LC_{50} of >20.5 mg/L in rats (Nuodex, Inc., 1979c, as cited by Versar, 2011). Assuming toxicity is related to the product of concentration and time (C x t), this study would indicate a 4-hour LC_{50} of > 5 mg/L. Because the actual inhalation LC_{50} is not known, **it is unclear whether DPHP fits the designation of acutely toxic under the FHSA** via the inhalation route.

DPHP causes at most minimal – slight skin irritation. It has been reported to cause no irritation in rabbits in one study (Nuodex, Inc., 1979d, as cited by Versar, 2011), slight irritation in rabbits in another study (BASF, 2002a, as cited by Versar, 2011 and ECHA, 2018b), and minimal irritation in guinea pigs (Nuodex, Inc., 1979e, as cited by Versar, 2011).

DPHP caused no eye irritation in rabbits in one study (Nuodex, Inc., 1979f, as cited by Versar, 2011), and slight to moderate but reversible eye irritation in another rabbit study (BASF, 2002b, as cited in NICNAS, 2003 and ECHA, 2018b).

DHPH does not appear to be a sensitizer. There was no evidence of sensitization in a repeated dermal application study in guinea pigs (Nuodex, Inc., 1979e, as cited by Versar, 2011 and ECHA, 2018b), and no QSAR alerts for sensitization.

The systemic toxicity of DPHP following repeated dosing is relatively low. The major effects observed in rats are decreased body weight and increased liver weight related to peroxisome proliferation. There are also sporadic reports of increased kidney weight, as well as thyroid hypertrophy, pituitary changes, and adrenal effects.

Anti-androgenic effects have not been reported with DPHP. There were no reproductive effects in the two-generation study (BASF AG, 2009, as cited by Bhat et al., 2014 and ECHA, 2018b).

DPHP is not a teratogen. Developmental effects were limited to soft tissue and skeletal variations (BASF, 2003, and as cited by Bhat et al., 2014 and ECHA, 2018b), and decreased pup body weight (BASF AG, 2009, as cited by Bhat et al., 2014 and ECHA, 2018b); the variations may have been secondary to maternal toxicity.

Based on the *in vitro* data, DPHP is not mutagenic and not clastogenic.

The data are insufficient to evaluate the carcinogenic potential of DPHP.

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APPENDIX 1. Search Terms Used

"di(2-propylheptyl) phthalate" OR "1,2-bis(2-propylheptyl) ester 1,2-Benzenedicarboxylic acid" OR "bis(2-propylheptyl) ester 1,2-Benzenedicarboxylic acid" OR "Bis(2-propylheptyl) phthalate" OR "Bis-(2-propylheptyl) phthalate" OR "DPHP" OR (53306-54-0)

APPENDIX 2. Explanation of Physico-chemical Parameters

The organic carbon normalized solid-water partition coefficient (K_{oc}), also known as the organic carbon adsorption coefficient, is defined as the ratio of the chemical's concentration in a state of sorption (i.e. adhered to soil particles) and the solution phase (i.e. dissolved in the soil water). K_{oc} is crucial for estimating a chemical compound's mobility in soil and the prevalence of its leaching from soil. For a given amount of chemical, the smaller the K_{oc} value, the greater the concentration of the chemical in solution. Thus, chemicals with a small K_{oc} value are more likely to leach into groundwater than those with a large K_{oc} value (http://www.acdlabs.com/products/phys_chem_lab/logd/koc.html).

Henry's law, one of the gas laws formulated by William Henry, states that "at a constant temperature, the amount of a given gas dissolved in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid (http://en.wikipedia.org/wiki/Henry's_law)." Henry's Law Constants characterize the equilibrium distribution of dilute concentrations of volatile, soluble chemicals between gas and liquid phases (http://www.epa.gov/athens/learn2model/part-two/onsite/esthenry.htm).

The octanol/water partition coefficient (K_{ow}) is defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. In recent years, this coefficient has become a key parameter in studies of the environmental fate of organic chemicals. It has been found to be related to water solubility, soil/sediment adsorption coefficients, and bioconcentration factors for aquatic life. Because of its increasing use in the estimation of these other properties, K_{ow} is considered a required property in studies of new or problematic chemicals (http://www.pirika.com/chem/TCPEE/LOGKOW/ourlogKow.htm).

The bioconcentration factor (BCF) is the concentration of a particular chemical in a tissue per concentration of chemical in water (reported as L/kg). This property characterizes the accumulation of pollutants through chemical partitioning from the aqueous phase into an organic phase, such as the gill of a fish. The scale used to determine if a BCF value is high, moderate or low will depend on the organism under investigation. The U.S. EPA generally defines a high potential BCF as being greater than 5,000; a BCF of moderate potential as between 5,000 and 100; a low potential BCF as less than 100 (http://en.wikipedia.org/wiki/Bioconcentration_factor; http://sitem.herts.ac.uk/aeru/footprint/en/Quest/ecotox.htm).