CPSC Staff Statement on University of Cincinnati Report
"Toxicity Review for Di (2-ethylhexyl) Sebacate (DEHS) and Dioctyl Sebacate (DOS)"[1]

June 2019

The U.S. Consumer Product Safety Commission (CPSC) contracted with the University of Cincinnati to conduct toxicology assessments for nine dialkyl o-phthalate (o-DAP) substitutes: phenyl esters of C10-C18 alkylsulfonic acid esters (ASE); glycerides, castor-oil-mono-, hydrogenated, acetates (COMGHA); dibutyl adipate (DBA) and di-isobutyl adipate (DiBA); di (2-ethylhexyl) sebacate (DEHS) and dioctyl sebacate (DOS); a mixture of 98% di-2-ethylhexyl terephthalate (DEHT) and 2% 2-ethylhexyl methyl terephthalate (2-EHMT); dibutyl sebacate (DBS); diisononyl adipate (DINA); epoxidized soybean oil (ESBO); and tributyl citrate (TBC). The reports will be used to inform staff's assessment of products that may contain these compounds 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 DEHS/DOS follows. Based on the research conducted by the University of Cincinnati, the animal data support the conclusion that DEHS/DOS does not appear to fit the designation of acutely toxic under the FHSA following single oral exposures. Data are not available to assess the acute toxicity of DEHS/DOS via the inhalation or dermal routes.

[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-ETHYLHEXYL) SEBACATE (DEHS)/
DIOCTYL SEBACATE (DOS)

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Table of Contents

1 Introduction

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with di (2-ethylhexyl) sebacate (DEHS)/dioctyl sebacate (DOS).

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 all dates to the date of the search (July, 2018). 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 DEHS/DOS and synonyms. Downloaded documents were saved as pdfs. The websites reviewed included:

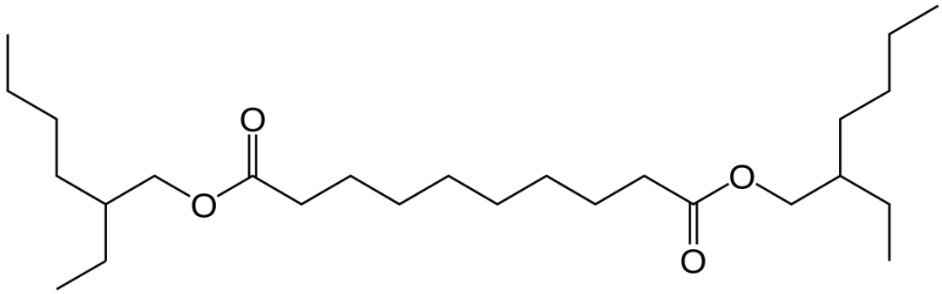
- ANSES Information on Chemicals (https://www.anses.fr/en)
- ChemIDPlus (https://chem.nlm.nih.gov/chemidplus/)
- ECHA Information on Chemicals (https://echa.europa.eu/information-on-chemicals)
- EFSA (https://www.efsa.europa.eu/)
- EPA chemistry dashboard (https://comptox.epa.gov/dashboard)
- EPA (https://www.epa.gov/)
- 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/)

2 Physico-Chemical Characteristics

Strictly speaking, the structure shown in Table 1 is named di(2-ethylhexyl) sebacate (DEHS), while dioctyl sebacate (DOS) refers to the straight-chain isomer (without the ethane side chains). (A more common name for the straight-chain isomer is dioctyl decanedioate, CAS number 2432-87-3.) However, there is some confusion in the literature with DEHS and DOS used somewhat interchangeably (BIBRA, 1996). Therefore, both DEHS and DOS are included in this assessment. However, where the documentation specifically uses one name, that name is used, and data on DOS were not included if the results clearly referred to the straight chain isomer.

Table 1: Physical and Chemical Properties of DEHS

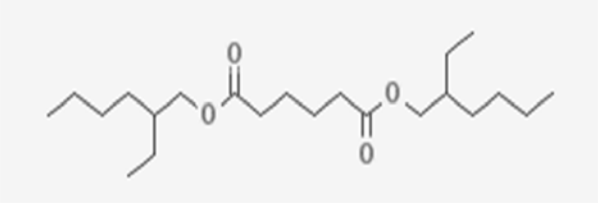
Chemical Name	Di(2-ethylhexyl)Sebacate/Dioctyl Sebacate
Synonyms	1-Hexanol, 2-ethyl-, sebacate;2-Ethylhexyl sebacate; Bis(2-ethylhexyl) decanedioate; Bis(2-ethylhexyl) sebacate; Decanedioic acid, bis(2-ethylhexyl) ester
CAS Number	122-62-3
Structure	
Chemical Formula	$C_{26}H_{50}O_4$
Molecular Weight	26.68 g/mol
Physical State	Liquid
Color	Pale straw-color
Melting Point	-48°C
Boiling Point	256°C at 5 mm Hg
Vapor Pressure	8.71 x 10^{-8} mm Hg

Water Solubility	1.21 x 10^{-11} mol/L
Log Kow	10.2 (estimated) (PubChem, 2018)
Log Koc[1]	1.01 x 10^{+4} L/kg (U.S. EPA, 2018a)
Henry's Law	9.20 x 10^{-8} atm-m^3/mole (U.S. EPA, 2018a)
Flashpoint	410°F
Density	0.868 g/mL
BCF	4 (estimated) (PubChem, 2018) 39.1 (predicted) (U.S. EPA, 2018a)
Source	HSDB (2018), unless otherwise stated

Log K_{ow} is the octanol-water partition coefficient. Henry's Law is Henry's Law Constant. Log Koc is soil adsportion coefficient. BCF is bioconcentration factor. See Appendix 2 for more details.

[1]It appears that this value is actually the Koc, not the Log Koc, based on its magnitude.

DEHS is closely related to di(2-ethylhexyl)adipate (DEHA), which differs from DEHS only in the number of carbons in the central core. Because toxicity is often due to the functional groups in a chemical, the toxicity of DEHS may resemble that of DEHA more than that of the related sebacate, dibutyl sebacate (DBS).



Structure of di(2-ethylhexyl)adipate (DEHA)

3 Manufacture, Supply, and Use

Manufacture and Supply

DEHS is a high production volume chemical with U.S. manufacture and imports reported between 1 and 10 million pounds (500 to 5000 tons) per year for 2015 (U.S. EPA, 2018b). DEHS is manufactured and/or imported in the European Economic Area at a rate of 1000 – 10,000 tons per year (ECHA, 2018a).

Use

DEHS is primarily used as a plasticizer for a variety of polymers (Oesterle-Deml, 1988). It has been found in toys and childcare articles on the Dutch market made with polyvinyl chloride (PVC), thermoplastic polyurethane (TPU), and polyethylene (PE) (FCPSA, 2008a, as reported by Maag et al. 2010; Abe et al., 2012). Industrial uses include as a lubricant and solvent (ECHA, 2018a). DEHS is used in vinyl flooring, wire and cable, stationery, wood veneer, coated fabrics, gloves, tubing, artificial leather, adhesives, paints, shoes, sealants, and carpet backing (Lowell

Center, 2011). It is also used in coatings, washing and cleaning products, plant protection products, sealants, polishes, waxes, machine wash liquids/detergents, automotive care products, personal care products, fragrances and air fresheners, electronic products, photographic supplies and film, and rubber (ECHA, 2018a; PubChem, 2018).

DEHS is used in food packaging films (Lowell Center, 2011) and is listed by FDA as an indirect additive used in food contact substances (FDA, 2018). Di Bella et al. (2018) detected DEHS in a variety of herbs and spices from Tunisia and Italy.

DEHS can be used to generate homogeneous, nontoxic aerosols, based on its relatively low boiling point, which allow it to be vaporized and recondensed onto solid nuclei to form uniformly-sized particles (Brain et al., 1996). These particles are very stable, based on the low vapor pressure of DEHS and that DEHS is not hygroscopic. Thus, evaporative losses are low, and the particles do not grow by adsorbing water in the lung. The stability of the resulting particles has meant that DEHS has properties making it useful for evaluating particle deposition in the lungs, as well as for evaluating respirator fit (Love et al., 1970).

4 Toxicokinetics

Very little information is available on the toxicokinetics of DEHS, aside from its metabolism. BIBRA (1996) cited an unpublished study (Fassett, 1981) reporting that DEHS is "not readily absorbed" through the skin of guinea pigs, but further details were not available. No studies were located that directly evaluated the distribution, metabolism or excretion of DEHS. However, Moody and Reddy (1978) inferred that DEHS is metabolized to 2-ethylhexyl alcohol, by comparison of the peroxisome proliferation effects seen with DEHS to those seen with 2-ethylhexyl alcohol, DEHA, and with other compounds that are metabolized to the 2-ethylhexyl moiety.

5 Hazard Information

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

The acute oral toxicity of DEHS/DOS is very low. In a nearly guideline-compliant study in male and female albino rats administered 5 mL/kg, the LD_{50} of DOS was >4560 mg/kg (based on a density of 0.912 g/mL) (Anonymous, 1976, as cited by ECHA, 2018a). In another study conducted generally according to test guidelines, a limit test with 5 female NMRI mice exposed to 2000 mg/kg did not result in any lethality, indicating an LD_{50} of >2000 mg/kg (Anonymous, 1994, as cited by ECHA, 2018a). Several other acute oral studies also reported high LD_{50} values, but minimal documentation was available in the secondary or tertiary sources available. In an unpublished report, the LD_{50} for rats and mice for DEHS was reported to be >12,800 mg/kg

(Fassett, undated; Fassett, 1981; Kustov et al., 1977, all as cited by BIBRA, 1996). Izmerov et al. (1977, as cited by BIBRA, 1996) reported an LD_{50} for DOS of 17,000 mg/kg in rats and 9500 mg/kg in mice. Clinical signs of toxicity were generally not reported in these studies, except that Kustov et al. (1977, as cited by BIBRA 1996) reported lethargy, reduced coordination, labored breathing, and diarrhea, with tissue damage in the liver, spleen, brain and heart. Further details were not available.

In a quantitative structure activity relationship (QSAR) evaluation using ACD/Pecepta, with a reliability index of 0.66 (moderately reliable), an LD_{50} of 26,000 was predicted for DEHS/DOS (species not specified) (Anonymous, 2013, as cited by ECHA, 2018a).

5.1.2 Acute Dermal Toxicity

The only reported acute lethality data for the dermal route was an LD_{50} of >10,000 mg/kg in guinea pigs treated with DEHS (Fassett, undated; Fassett, 1981, both as cited by BIBRA, 1996). Further details were not available.

5.1.3 Acute Inhalation Toxicity

DEHS has been used in controlled exposures to evaluate respirator fit and evaluate aerosol deposition in the human lung (BIBRA, 1996). Although the exposure was for very short periods and exposure concentrations were not available, this intended controlled exposure supports the conclusion that the acute inhalation toxicity of DEHS is low.

Izmerov et al. (1977, as cited by BIBRA, 1996) reported that exposure to 60 mg/m^3 DOS was the threshold for irritation of the upper respiratory tract and eyes of humans; no further details were available.

Several acute studies have been conducted via the inhalation route, but the information available in the secondary sources is generally limited. Fassett (undated; Fassett, 1981, both as cited by BIBRA, 1996) exposed three rats to saturated DEHS vapor for 6 hours, and did not observe lung toxicity (or, presumably deaths); further details were not available. There was also no effect on lung or liver (and presumably no deaths) among rats (number not reported) exposed to concentrations up to 250 mg/m^3 for 4 hours (Rubin et al., 1983; Swift, 1983, as cited by BIBRA, 1996).

In a study focusing on the toxicity of thermal decomposition products of DEHS, Treon et al. (1955) reported no lethality in a cat, guinea pigs, rabbits or rats exposed to a measured concentration of 1140 mg/m^3 DEHS for 7 hours. Further details about this study are provided in Section 5.2, Short-Term Toxicity. In contrast, exposure for 7 hours to a mist produced by heating DEHS to 700 ºF (371ºC) (nominally 940 mg DEHS/m^3) resulted in lethality. Deaths were observed in two of four rabbits, three of four rats, but not in the two exposed guinea pigs. Lethality of the thermal decomposition products increased with increasing temperature, and the order of lethality in various tests was consistently rats > rabbits > guinea pigs. This study was conducted prior to modern testing methods, did not report the length of monitoring after exposure, and did not use modern methods of test material generation or monitoring.

Nervous system effects (but presumably no lethality) were observed in rats exposed to 600 mg/m^3 DOS for 4 hours, but an unspecified number of deaths were reported after exposure to 800 mg/m^3 DOS (Izmerov et al., 1977, as cited by BIBRA, 1996). Further details were not available.

ECHA (2018a) reported on a read-across evaluation in a category approach from an unidentified substance, based on a generally well-documented study. Male and female Sprague-Dawley rats (5/sex) were exposed for 4 hours to the highest practical concentration, 3.2 mg/L, and sacrificed the day after exposure. The LC_{50} was >3.2 mg/L

5.1.4 Irritation/Sensitization

DOS was not irritating when an unspecified volume of neat solution was applied to the skin of 15-30 volunteers for 48 hours (described by BIBRA, 1996 as a covered test) (Mallette and Von Haam, 1952).

In an animal test of dermal irritation, undiluted DOS was applied to the shaved and abraded skin of three male and three female rabbits (Anonymous, 1976, as cited by ECHA, 2018a). The study was conducted generally according to OECD Guideline 404, except that exposure was for 24 hours, the site was occluded, and the rabbits were examined at 24 and 72 hours after patch removal. The erythema score and edema score were both 0 on a scale of 0 to 4, and the authors concluded that DOS is not irritating. In another study for which the basic key data were provided (Anonymous, 1994, as cited by ECHA, 2018a), three male New Zealand White rabbits were treated with an unspecified amount of DOS and monitored for up to 8 days. Erythema was noted in all three rabbits (average scored at 24, 48 and 72 hours, 1 on scale of 0 to 4), but there was no edema. The study authors also considered DOS non-irritating.

Among 15-30 volunteers treated with an unspecified dose of neat DBS for 48 hours, no sensitization was observed when the subjects were re-exposed 2 weeks later (Mallette and von Haam, 1952). A single subject who had been sensitized to di-isopropyl sebacate and cross-reacted to diethyl sebacate and dibutyl sebacate did not react to DOS at concentrations up to 10% in petrolatum or in PEG-300 (De Groot et al., 1991). No other details were available, but BIBRA (1996) suggested that the treated duration was for 48 hours. Fassett (undated, as cited by BIBRA, 1996) reported that DEHS (presumably neat) was not irritating to the skin of guinea pigs.

Mallette and Von Haam (1952) observed no skin irritation in a group of two to four rabbits dermally treated with an unspecified volume of neat DEHS for 48 hours. In addition, no sensitization was observed when the rabbits were challenged 2 weeks later with neat DEHS.

In a QSAR analysis (Anonymous, 2013, as cited by ECHA, 2018a), DEHS was not a skin sensitizer according to Toxtree, but it was a sensitizer according to Vega; the consensus conclusion was listed as “skin sensitizer.” Read-across analyses from DEHA were negative, based on negative results in guinea pigs injected intracutaneously with 0.1% DEHA in olive oil

three times/week for 3 weeks, and challenged after a 2-week rest period (Kolmar Research Center, 1967, as cited by ECHA, 2018a).

5.2 Short-Term Toxicity

Treon et al. (1955) exposed one cat, two guinea pigs, two rabbits and four rats to a measured concentration (based on a single collected sample) of 1140 mg/m^3 DEHS for 7 hours on 10 days, and did not observe any lethality. It was not clear whether the exposure days were consecutive or were 5 days/week. This study was conducted prior to modern testing methods, did not report the length of monitoring after exposure, and did not use modern methods of test material generation or monitoring. No information was provided on any clinical signs of toxicity or any other evaluation of toxicity.

5.3 Repeated Dose Toxicity

Repeated dose toxicity data on DEHS/DOS are very limited.

Moody and Reddy (1978) evaluated the effects of DEHS on the liver as part of an investigation of peroxisome proliferation. Male F-344 rats received 2% DEHS (four rats, 13 controls) or other compounds (4-7 rats/compound) in the diet for 3 weeks, corresponding to about 2000 mg/kg-day, based on a food factor of 0.1 for a subchronic study with a F344 rat (U.S. EPA, 1988). There was no effect on body weight, but relative liver weight was significantly ($p<0.001$) increased. Liver catalase activity, liver carnitine acetyltransferase activity and hepatic peroxisome proliferation were all increased. DEHA and di-(2-ethylhexylphthalate) (DEHP), as well as 2-ethylhexanol and 2-ethylhexanoic acid, were all also tested at 2% in the diet, and also produced peroxisome proliferation. The potency (on a weight basis) of DEHP was generally similar to but slightly higher than that of DEHA and DEHS; DEHA and DEHS were generally comparable. The straight-chain molecules hexyl alcohol, hexanoic acid and hexyl aldehyde did not induce peroxisome proliferation, even at doses up to 8% in the diet. These results suggested that the peroxisome proliferation resulted from formation of the 2-ethylhexyl alcohol metabolite. Furthermore, the straight-chain compound DOS would not form the branched ethylhexyl moiety, and so would not be expected to cause peroxisome proliferation. While 2% in the diet was an effect level, only the liver was evaluated and only one dose level was tested, and so this study is inadequate for identifying a NOAEL or LOAEL.

In an inhalation study in which groups of 12 rats were exposed to DEHS vapor up to 250 mg/m^3 for 4 hours/day, 5 days/week for 13 weeks, there were no adverse systemic effects or effects on the lungs (Swift, 1983, as cited by BIBRA, 1996). This is a citation based on a personal communication, and no further details are available.

5.4 Chronic Toxicity/Carcinogenicity

BIBRA (1996) cited a secondary reference of an unpublished study (Le Breton, 1968), in which rats were fed 200 ppm DOS in the diet (about 10 mg/kg-day, assuming a food factor of 0.05) for

up to 19 months. The study reported that there were no gross or microscopic abnormalities. Further details on this study are not available.

5.5 Reproductive Toxicity

In a four-generation study of rats fed 200 ppm DOS in the diet (about 10 mg/kg-day, assuming a food factor of 0.05), reproduction, suckling and growth were "evidently normal" (Le Breton, 1968, as cited by BIBRA, 1996). No further details were available.

In a QSAR analysis using the Leadscope software (Anonymous, 2013, as cited by ECHA, 2018a), DEHS was negative for male and female reproductive toxicity. The prediction was considered reliable even though there were few compounds structurally similar to the target chemical in the training database, because the target chemical is sufficiently well-described by the models.

5.6 Prenatal, Perinatal, and Post-natal Toxicity

No developmental toxicity studies of DEHS were identified. The analogue DEHA was not a teratogen, but did cause decreased litter weight and minor variations (ICI, 1988a, 1988b, as cited by ECHA, 2018b).

5.7 Genotoxicity

DEHS was negative for gene mutation in *Salmonella typhimurium* strains TA 1535, TA 100, TA 1537 and TA 98 in the presence and absence of Aroclor 1254-induced Syrian hamster liver S9 and Aroclor 1254-induced rat liver S9 (Zeiger et al., 1985).

DEHS was negative for mutagenicity with high reliability using several different QSAR software packages (Anonymous, 2013, as cited by ECHA, 2018a). DEHS was negative but with somewhat lower reliability in QSAR prediction for chromosome aberration *in vivo.* Other ECHA (2018a) entries did read-across from DEHA.

5.8 Mechanistic Studies

DEHS was negative for promotion activity in the rat liver foci bioassay (Oesterle and Deml, 1988). In this study, Sprague-Dawley rats (5/sex/dose) were administered a single initiating dose of 8 mg/kg diethylnitrosamine (DEN) by gavage, followed by promotion with DEHS by gavage three times/week at 500 mg/kg/dose for 11 consecutive weeks. Control groups received DEHS alone or olive oil vehicle. DEHS did not increase the incidence of gamma-glutamyltrasnpeptidase (GGT)-positive foci, and did not affect liver weight or body weight. DEHP was tested in the same assay at 200 and 500 mg/kg and exhibited weak promoting activity.

Brain et al. (1996) instilled DEHS at 37 mg/kg body weight into the lungs of male Syrian golden hamsters (6/group), sacrificed the hamsters 24 hours later, and conducted lung lavage to evaluate

markers of inflammation and other types of lung toxicity. Three different samples of DEHS were evaluated, including both untreated ("fresh") and heated DEHS. Increased polymorphonuclear leukocytes (PMNs) and small decreases in macrophages were seen with all three samples, but none of these changes were statistically significant. This suggests that there may have been some slight inflammation and macrophage cytotoxicity, but the degree of change was not biologically meaningful. There was no increase in albumin (a subtle measure of damage to the air-blood barrier), no effect on macrophage function (as measured by lamda phage phagocytosis), and no increase in red blood cells in the lavage fluid (a measure of alveolar hemorrhage). There was also no significant increase in cell enzymes in the extracellular supernatant of the lavage fluid (lactate dehydrogenase, peroxidase, β-*N*-acetylglucosaminidase) indicative of cell damage. Although this study used a nonphysiological exposure route, the administration technique represents a worst-case scenario, and the study tested a number of sensitive measures of lung toxicity. Therefore, the absence of significant findings supports the conclusion that DEHS is has very low toxicity to the respiratory tract via the inhalation exposure route. Systemic toxicity was not evaluated in this study.

5.9 Mode of Action

In light of the limited data on adverse effects seen with DEHS, a completed MOA evaluation is not possible. However, DEHS can be metabolized to 2-ethylhexanol, and is a peroxisome proliferator (Moody and Reddy, 1978). Aside from increased liver weight, peroxisome proliferation-related effects have not been evaluated with DEHS. Note that the 2-ethylhexyl moiety cannot be formed from straight-chain di-octyl sebacate (DOS), indicating that differences in toxicity would be expected between the straight-chain and branched compounds.

DEHS was negative for promotion activity in the rat liver foci bioassay (Oesterle and Deml, 1988). DEHS was not mutagenic to bacteria (Zeiger et al., 1985), and limited QSAR data suggest that it is negative for genotoxicity (Anonymous, 2013, as cited by ECHA, 2018a).

5.10 Lowest Hazard Endpoints by Organ System and Exposure Duration

The repeat dose toxicity data for DEHA are extremely limited, and consist of studies that either evaluated only a limited number of endpoints, or for which only limited details are available. Exposure to DEHS in the diet for 3 weeks (about 2000 mg/kg-day) caused increased liver weight and peroxisome proliferation in rats (Moody and Reddy, 1978). However, only one dose level was tested and only the liver was evaluated, and so the study was insufficient to identify an effect level. No gross or microscopic pathology was seen in rats fed about 10 mg/kg-day in the diet for up to 19 months, but few study details are available, and only one dose was tested (Le Breton, 1968, as cited by BIBRA, 1996). In another poorly documented study, there were no adverse systemic effects or effects on the lungs in rats exposed to DEHS vapor up to 250 mg/m^3 for 4 hours/day, 5 days/week for 13 weeks (Swift, 1983, as cited by BIBRA, 1996).

A QSAR analysis using the Leadscope software (Anonymous, 2013, as cited by ECHA, 2018a) concluded that DEHS was negative for male and female reproductive toxicity. The only reproductive toxicity study of DEHS tested a relatively low dose (10 mg/kg-day), and was very

briefly reported. Therefore, the experimental data are insufficient to provide information on the reproductive toxic potential of DEHS.

No developmental toxicity studies of DEHS were identified, although read-across from DEHA suggests the potential for decreased litter weight and minor variations (ICI, 1988a, 1988b, as cited by ECHA, 2018b). However, this approach cannot inform the dose-response for this endpoint.

The data suggest that DEHS is not genotoxic, based on the negative results in bacteria (Zeiger et al., 1985) and limited QSAR data (Anonymous, 2013, as cited by ECHA, 2018a).

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

5.11 Uncertainties and Data Gaps

The data gaps for DEHS are substantial, since the toxicity data obtained using standard methods are limited to acute exposures. Toxicokinetic data, particularly absorption data, on DEHS are lacking, as well as studies on repeated-dose toxicity that evaluated a range of endpoints, chronic toxicity/carcinogenicity, reproductive toxicity, developmental toxicity, and genotoxicity. In addition, the studies that are available were generally reported with few details.

In light of the lack of systemic effects, there are no uncertainties related to interpretation of the hazard data. There is some uncertainty, however, regarding whether the DOS studies were with DEHS or the straight-chain DOS.

6 Exposure

The use of DEHS in consumer products has been described in Section 3 of this report. The general population may be exposed to DEHS via dermal contact with consumer products, oral contact via mouthing of products (e.g., children's toys), by the ingestion of food or beverages containing this compound, by ingestion of foods stored in plastic materials containing DEHS, by ingestion or dermal contact with contaminated household water supplies, and by inhalation. Occupational exposure to DEHS may occur through inhalation or dermal contact (HSDB, 2018).

Bui et al. (2016) reported an estimated intake rate for DEHS calculated by Stuer-Lauridsen et al. (2001, as cited by Bui et al., 2016) using the EASE (Estimation and Assessment of Substance Exposure) model. The estimate was 4.36×10^{-3} µg/kg-day for inhalation, oral and dermal uptake combined; the specific population and activity were not identified. Bui et al. (2016) noted that the intake rates for alternative plasticizers are not based on biomonitoring data and that important uptake routes may not have been included due to lack of studies measuring exposure.

Abe et al. (2012) measured plasticizers in 101 samples of PVC toys on the Japanese market. They found DEHS in 2% of the samples ("not designated toys" [1]) with a mean concentration

[1] Japanese publication with abstract and tables only in English. We assumed "designated" refers to those toy types that are defined as "designated toys" in Article 78 of the Ordinance for Enforcement of the Food Sanitation Act (revised in March 2008) (https://www.jetro.go.jp/en/reports/regulations/pdf/foodext201112e.pdf). "Designated toys"

(detected samples only) of 0.08%. A 2007 survey in the Netherlands of soft plastic toys (n=200) and childcare articles (n=12) found DEHS in 0.6% of sampled items (FCPSA 2008a, as As cited by Maag et al., 2010).

DEHS is listed by FDA as an indirect additive used in food contact substances (FDA, 2018). Di Bella et al. (2018) measured 18 plasticizers and BPA residues in a variety of herbs and spices from Tunisia and Italy. DEHS was not detected frequently, but when it was, it was at levels much higher than the other plasticizers. The mean residue level of DEHS in the spices where it was detected ranged from 1.12 (+/- 0.86) µg/kg to 3.16 (+/-0.89) µg/kg. The authors speculated the source of contamination was pollution or farming methods.

DEHS was identified, but not quantified, in one drinking water sample from the Delaware River (Lucas, 1984, Sheldone and Hites, 1978; as cited by HSDB, 2018). Weschler and Shields (1986) reported a concentration of 2 ng/m^3 in the indoor air of U.S. office buildings (as cited by HSDB, 2018).

Occupational exposure to DEHS may occur through inhalation or dermal contact with the compound where it is produced or used; an estimated 3135 workers are potentially exposed in the U.S. (NIOSH 1983, as cited by HSDB, 2018).

7 Discussion

7.1 Toxicity Under FHSA

Animal data support the conclusion that **DEHS does not appear to 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. An acute LD_{50} value in rats was reported as >4560 mg/kg (Anonymous, 1976, as cited by ECHA, 2018a), but that was for "DOS," and it is not clear if the data were based on the linear form or DEHS. Several other acute oral studies also reported high LD_{50} values, but minimal documentation was available in the secondary or tertiary sources available. These included LD_{50} values in rats of >12,800 mg/kg (Fassett, undated; Fassett, 1981; Kustov et al., 1977, all as cited by BIBRA, 1996), and 17,000 mg/kg (Izmerov et al., 1977, as cited by BIBRA, 1996. Together these data support the conclusion that the DEHS LD_{50} is >5000 mg/kg. A definitive conclusion is not possible for the dermal route, since DEHS has not been tested for acute lethality on rabbits. However a very high dermal LD_{50} of >10,000 mg/kg was reported in guinea pigs (Fassett, undated; Fassett, 1981, both as cited by BIBRA, 1996). Although limited details were available, this study suggests that toxicity in rabbits may also be low. Data are not available to assess the acute toxicity of DEHS via the inhalation route.

include those toys intended to come into direct contact with an infant's mouth, infant jewelry, decal sticker toys, rolly-polies, masks, origami, rattles, intellectual development facilitating toys, wooden blocks, toy telephones, toy animals, dolls, clay, toy vehicles, balloons, toy building bricks, balls, housekeeping toys, and toys to be played with in combination to those types of toys listed.

DEHS was not irritating to the skin of volunteers (Mallette and von Hamm, 1953), and minimally irritating to rabbits (Anonymous, 1994, as cited by ECHA, 2018a). DEHS was also not a sensitizer in humans or in rabbits (Mallette and von Hamm, 1952). However, none of these studies were conducted according to modern test methods and only limited details are available.

Data are insufficient to assess the repeated dose toxicity of DEHS, and its potential to cause reproductive or developmental toxicity, genotoxicity, or cancer. Read-across from the related compound DEHA may be possible for these endpoints.

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APPENDIX 1

Search Terms Used

Toxline: "Dioctyl sebacate, Di(2-ethylhexyl)sebacate" OR "Di(2-ethylhexyl)sebacate" OR "Dioctyl sebacate" OR "Bis(2-ethylhexyl) sebacate" OR "Bis(2-ethylhexyl)decanedioate" OR "bis(2-ethylhexyl) ester decanedioic acid" OR "Di-2-ethylhexyl sebacate" OR "1,10-bis(2-ethylhexyl) ester decanedioic acid" OR "bis(2-ethylhexyl) ester sebacic acid" OR "2-ethyl-1-hexanol sebacate" OR "2-Ethylhexyl sebacate" OR "Bis(2-ethylhexyl) decanedioate" OR "Diethylhexyl sebacate" OR "Dioctyl sebacate" OR "Bisoflex" OR "Edenor DEHS" OR "Ergoplast SDO" OR "Monoplex DOS" OR "Octoil S" OR "Plexol" OR "Staflex DOS" OR "Uniflex DOS"; 122-62-3

Pubmed: (122-62-3) OR "Di(2-ethylhexyl)sebacate" OR (Dioctyl sebacate) OR (Bis(2-ethylhexyl) sebacate) OR "Di-2-ethylhexyl sebacate" OR (2-Ethylhexyl sebacate) OR (Diethylhexyl sebacate)

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 as the ratio between gas and liquid phases.

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).