CPSC Staff Statement on University of Cincinnati Report "Toxicity Review for Di-2-ethylhexyl Terephthalate (DEHT)"[1]

October 2018

The U.S. Consumer Product Safety Commission (CPSC) contracted with the University of Cincinnati to conduct toxicology assessments for six dialkyl o-phthalate (o-DAP) substitutes: acetyl tri-n-butyl citrate (ATBC); bis(2-ethylhexyl) adipate (DEHA); di-2-ethylhexyl terephthalate (DEHT); 1,2-cyclohexanedicarboxylic acid, dinonyl ester, branched and linear (DINX); trioctyltrimellitate (TOTM); and 2,2,4-trimethyl-1,3-pentanediol-diisobutyrate (TPIB). 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 a quantitative assessment of exposure and risk is performed to evaluate whether a specified product may be considered a "hazardous substance".

The toxicity review for DEHT follows.

[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 TEREPHTHALATE
(DEHT)

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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-ethylhexyl terephthalate (DEHT). It is an update of a previous contractor report to CPSC (Versar, 2010).

Literature searches for physico-chemical, toxicological, exposure, and risk information were performed in November 2017 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 of the PubMed and Toxline databases covered all dates through the date of the search (November, 2017). However, studies dated up to 2007 were screened out of the library during the screening process using the Endnote files, as the current report supplements and updates a staff report prepared in 2010 (Versar, 2010). Other databases and websites were also used to identify additional key information, particularly authoritative reviews. Searches for authoritative reviews addressing general toxicity and physicochemical information were conducted with the following databases using the CAS number for DEHT and synonyms. 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 (https://www.epa.gov/)
- EPA chemistry dashboard (https://comptox.epa.gov/dashboard)
- EPA IRIS (https://www.epa.gov/iris)
- FDA (https://www.fda.gov/)
- Google
- Health Canada (https://www.canada.ca/en/health-canada.html)
- IARC (https://www.iarc.fr/)
- INCHEM (http://www.inchem.org/)

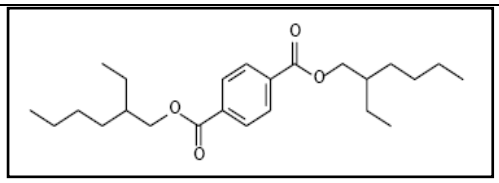
- JEFCA (http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/)
- NICNAS (https://www.nicnas.gov.au/)
- NTP (https://ntp.niehs.nih.gov/)
- OECD (http://www.oecd.org/)
- WHO (http://www.who.int/en/)

The only new DEHT toxicology study was an acute inhalation toxicity study (ANSES, 2015; no citation to original study). New studies that were found in the primary literature also included studies on toxicokinetics, mechanism, and exposure, as well as several reviews. Several of the key toxicity studies were unpublished and not available as the primary studies. Therefore, these studies were evaluated based on authoritative reviews and data compilations, including OECD (2003), Eastman Chemical (2010), Ball et al. (2012), and ANSES (2015).

2 Physico-Chemical Characteristics

Some physical and chemical properties of DEHT are summarized below in Table 1.

Table 1: Physicochemical Properties and Identification Information for Di-2-ethylhexyl Terephthalate

Chemical Name	Di-2-ethylhexyl terephthalate (DEHT)
Synonyms	Bis(2-ethylhexyl) terephthalate; Di-(2-ethylhexyl) terephthalate; 1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester; 1,4-Benzenedicarboxylic acid, 1,4-bis(2-ethylhexyl) ester; ADK Cizer D 810; DEHTP; Dioctyl terephthalate; DOTP; Eastman 168; Kodaflex DOTP; NEO-T; Palatinol DOTP; Plasticizer 168; Terephthalic acid, bis(2-ethylhexyl) ester; UN 488
CAS Number	6422-86-2
Structure	 (SCENIHR, 2008)
Chemical Formula	$C_{24}H_{38}O_4$
Molecular Weight	390.556 g/mol
Physical State	Liquid
Color	Colorless
Melting Point	-48°C; <-67.2 ^{0}C
Boiling Point	375°C at 101.325 kPa
Vapor Pressure	< 0.001 Pa
Water Solubility	0.4
Log Kow	5.72 (Remberger et al., 2005); As high as 8.39 (Danish EPA, 2010)
Flashpoint	212°C at 101.325 kPa

Source	IUCLID (unless otherwise stated)

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

DEHT is listed under the U.S. EPA's Toxic Substances Control Act (TSCA) as 1,4-benzenedicarboxylic acid, di(2-ethylhexyl) ester; however, it is commonly referred to (informally) as either di(2-ethylhexyl) terephthalate or dioctyl terephthalate (DOTP) (McMillan, 2004). DEHT is produced by Eastman Kodak Company under the name Eastman 168 Plasticizer.

Because "phthalate" is part of one of the common names for DEHT, it can be confused with "phthalate esters," the common name for the class of compounds known as dialkyl *ortho*-phthalates *(o*-DAPs). While *ortho*-phthalates contain two adjacent ring substitutions, *para*-phthalates, such as DEHT, have substitutions occupying positions 1 and 4 (located "across from" each other on the ring). Therefore, DEHT is not an *o*-DAP chemical, and thus is not subject to specific U.S. EPA or CPSC regulations aimed as these compounds. *Ortho*-phthalates are metabolized to a monoester form, which scientists generally agree to be the active metabolite (the cause of toxicological effects observed). In contrast, available data indicate that metabolism of DEHT (as reported by Eastman) does not lead to significant formation of a monoester (McMillan, 2004).

DEHT is soluble in water at up to 4.0 mg/L. It is expected to bind tightly to particulate matter and sediment in the water column, based on its estimated Koc value of 870,000, and is expected to be essentially immobile in soil (HSDB, 2008). Based on a Henry's Law constant of 1.02 x 10-5 atm m^3/mol (Remberger et al., 2005), DEHT will volatilize slowly from water surfaces and may also volatilize from moist soil surfaces. Biodegradation in soil is expected to be a major fate process for DEHT, based on results for the structurally similar plasticizer DEHP, which undergoes aerobic and possibly anaerobic biodegradation (HSDB, 2008). If released to the atmosphere, DEHT will exist in both the vapor phase and the particulate phase, based on an estimated vapor pressure of 2.14 x 10^{-5} mm Hg at 25ºC. Particulate-phase DEHT may be removed physically from air by wet and dry deposition (HSDB, 2008).

Based on estimated BCF values ranging from 25 (HSDB, 2008) to approximately 400 (Eastman Chemical, undated; ANSES, 2015)[2], DEHT is not expected to bioconcentrate in aquatic organisms. ANSES (2015) noted that the BCF of 393 L/kg was based on a study in a saltwater mollusk, and that the data cannot be extrapolated to fish, due to the active surface properties of DEHT. However, these BCF values are supported by the measured BCF of 637 for structurally similar DEHP. DEHP also had a depuration half-life of 38 days in sheepshead minnow, indicating that DEHT also may be readily metabolized by some organisms (HSDB, 2008).

[2]Versar (2010) reported the BCF as 1,400,000, citing Remberger et al. (2005), but that reference was not available for review. This high BCF is also inconsistent with the data reported by other sources, and inconsistent with the analogy to DEHP.

3 Manufacture, Supply, and Use

Manufacture

DEHT is produced by transesterification of dimethyl terephthalate with 2-ethylhexanol (HSDB, 2008).

Supply

Di(2-ethylhexyl) terephthalate (DEHT) is a U.S. EPA high production volume chemical, with production above 50 million pounds/year in the U.S. (SCENIHR, 2008). Because it can be used as a substitute for DEHP, and other regulated or restricted plasticizers, consumption volume is increasing. US consumption rose from 11,000 metric tons in 1990 to 48,000 metric tons in 2012. Similarly, Western European consumption rose from 2000 metric tons in 2002 to 45,000 metric tons in 2012, and was expected to reach approximately 90,000 metric tons by 2018 (Bizzari et al., 2013, as cited by Lessermann et al., 2016).

Use

DEHT is compatible with cellulose acetate-butyrate, cellulose nitrate, polymethyl methacrylate, polystyrene, polyvinyl butyral, and polyvinyl chloride resins (HSDB, 2008). Essentially 100% of DEHT produced is used as a plasticizer and softener for these polymers (HSDB, 2008). It has a wide range of applications including beverage closures, and sealing materials used in construction joints (HSDB, 2008; SCENIHR, 2008). The 2008 European Commission Report (SCENIHR, 2008) states that it is used in children's toys and child care articles, based on a submission from the DEHT manufacturer, Eastman Chemical Co. However, no specific toys or toy manufacturers were identified, so this remains unconfirmed. TURI (2006) noted that DEHT can effectively be substituted for DEHP in resilient flooring, but not rubber mats. Other uses include shoe soles, weather stripping, water-proofing for coated fabrics, and vinyl gloves (ANSES. 2015; OECD, 2003). OECD (2003) also noted that DEHT is useful as a plasticizer for polyvinyl chloride (PVC) when low volatility, low migration, and flexibility at low temperatures are desired.

4 Toxicokinetics

Absorption

The key study characterizing *in vivo* absorption and metabolism of DEHT by the oral route is Barber et al. (1994). In this study, Barber et al. administered a radio-labeled dose of 100 mg/kg-bw DEHT by gavage (in corn oil) to 10 adult male SD rats. Absorption of DEHT was rapid following oral administration. At least 35% of the administered dose was absorbed, based on the

percent of the radioactivity found in the urine and exhaled CO_2. (See the text under elimination below.)

In another study, percutaneous absorption was low following dermal application of radiolabeled DEHT onto human skin, with an absorption rate of 0.103 µg/cm^2/hr (Guerin and Taylor, 2002; as cited by OECD, 2003; Eastman Chemical, 2010). Eastman Chemical (2010) calculated that a 1 hour exposure of both hands would result in a systemic dose of 1.06 µg/kg.

Distribution

In the Barber et al. (1994) study, only a small fraction (<2%) of the administered dose remained in the carcass at sacrifice 6 days after dosing, primarily in the liver and fat.

Metabolism

Lessmann et al. (2016b) investigated the metabolism and renal excretion following dosing of three adult volunteers with 50 mg DEHT (actual doses 0.55 – 0.59 mg/kg bw). Full urine samples were collected for 48 hours, beginning immediately prior to dosing. It appears that the authors focused on metabolites unique to DEHT, since terephthalic acid (TPA) was not monitored, and no mass balance was conducted. Instead, the authors focused on the four metabolites 1-mono-(2-ethyl-5-hydroxy-hexyl) benzene-1,4-dicarboxylate (5OH-MEHTP), 1-mono-(2-ethyl-5-oxo-hexyl) benzene-1,4-dicarboxylate (5oxo-MEHTP), 1-mono-(2-ethyl-5-carboxyl-pentyl) benzene-1,4-dicarboxylate (5cx-MEPTP), and 1-mono-(2-carboxyl-methyl-hexyl) benzene-1,4-dicarboxylate (2cx-MMHTP). In a related pilot biomonitoring study, Lessmann et al. (2016a) sampled urine from 34 male and female volunteers (aged 25–61) not known to be occupationally exposed to DEHT, and detected 5cx-MEPTP above the limit of quantification in 94% of the samples (median: 0.9 µg/L, maximum: 38.7 µg/L). In other biomonitoring studies, the monoester mono-2-ethylhydroxyhexyl terephthalate (MEHHTP) has been identified in human urine (Silva et al., 2015; Silva et al., 2017). The oxidative metabolite mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP) has also been detected in human urine (Silva et al., 2017)

In *in vitro* studies using intestinal homogenates, Barber et al. (1994) showed that DEHT is rapidly (half-life = 53 minutes) hydrolyzed to TPA, 2-ethylhexanol (2-EH) and smaller amounts of the monoester mono(2-ethylhexyl) terephthalate (MEHT). A recent *in vitro* study by Silva et al. (2015) described side chain oxidized monoesters that are also minor metabolites of DEHT. Whereas TPA and 2-ethylhexanol can be formed by various other chemicals, the monoester-derived metabolites are specific to DEHT, and can be used for biomonitoring, as noted for the studies discussed above.

Elimination

In the Barber et al. (1994) study, approximately 93 % of the total radioactivity was recovered within 24 hours of administration, with most of the dose recovered from the feces (56.5%) and urine (31.9%); 3.6% was expired as CO_2. The mean amount of unchanged radioactive DEHT recovered in the feces was 36.6%, with 50.5% recovered as TPA in the urine. In total, 91.7 % of the dose could be accounted for as either unchanged DEHT (in feces), unlabeled TPA (in urine) or exhaled CO_2. This mass balance limits the amount of DEHT converted and mono(2-ethylhexyl) terephthalate (MEHT) and its metabolites, to a maximum of 9.3 % of orally administered dose.

In the Lessman et al. (2016b) study, times for maximal concentrations in the urine ranged from 4.2 hours to 5.2 hours, and elimination half-times for the metabolites were all very similar, at 6.9-7.0 hours. The urinary excretion factors (Fue) of the four metabolites as percentages of the applied dose were as follows: 5cx-MEPTP, 12.95%; 5OH-MEHTP, 1.82%; 5oxo-MEHTP, 1.01%; 2cx-MMHTP, 0.28%. The study authors noted that these urinary excretion factors could be used to back-calculate DEHT intake (assuming it is all from the oral route).

5 Hazard Information[3]

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

Eastman Kodak Co. (1975) reported an oral LD_{50} value of >3200 mg/kg DEHT in both rats and mice (as cited in Versar, 2010; Eastman Chemical, 2010; Ball et al., 2012). No signs of mortality, irritation or distress were observed in either species during a 14-day observation period following oral treatment. No other details were reported for this study. The European Commission (SCENIHR, 2008) Safety Evaluation reported an oral LD_{50} of 5000 mg/kg, but did not provide a reference and no data matching this lethal dose were found during this review[4]. A Russian study summarized in RTECS did not attain an LD50 in mice receiving DEHT up to 20,000 mg/kg, but the mice that did die during the study exhibited excitation followed by CNS inhibition (Timofiyevskaya, 1982).

[3] Where available, this report provides significance level p values in all sections. However, source secondary references often report only that a change was significant without reporting the p level. 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.

[4] In other documents (e.g., Danish EPA assessment of DEHT) the source is indicated as "TSCA FHSA Regulations (1979): 16 CFR Part 1500.40". However, this code pertains to toxicity testing methods and the cited information does not appear in the indicated source. The Federal Register 1982, 47(233) (see section 2.2.b Bis(2-Ethylhexyl) Terephthalate) contains relevant information on DEHT toxicity. It is possible that this LD_{50} reflects a typographical error and should have been LD_{50} *greater than* 5000 mg/kg, as was reported by Eastman Chemical (2010).

5.1.2 Acute Dermal Toxicity

Eastman Kodak Co. (1975, as reported by Versar, 2010; Ball et al., 2012) reported a study in which DEHT at 5, 10 or 20 mL/kg (~4920, 9840 or 19,680 mg/kg based on a density of 0.984 g/mL) was applied to the depilated skin of Duncan-Hartley guinea pigs (one male/dose) under occluded conditions for 24 hours. No signs of systemic toxicity were reported during the 14-day observation period and the resulting 24-hour dermal LD50 in guinea pigs was >20 mL/kg (>19,680 mg/kg).

5.1.3 Acute Inhalation Toxicity

No single-exposure inhalation study was located.

5.1.4 Irritation/Sensitization

Lockhart (2001a, as reported by Versar, 2010; ANSES, 2015; OECD, 2003) reported that 18 human subjects (9 men and 9 women) were exposed to DEHT applied in semi-occlusive patches (dose not reported). Patches were applied for 24 hours every other day for a five day period (applied on Days 1, 3, and 5). Twenty-four hours after removing the patches, prior to patch reapplication, skin sites were scored for irritation. Only minimal irritation was observed that was not considered related to the substance since the effect did not increase in a dose-dependent manner.

DEHT was tested for dermal irritation and sensitization in 203 men and women volunteers ranging in age from 18 to 81 years (David et al., 2003). Subjects were exposed to 0.5% (v/v) DEHT under a semi-occlusive patch for 24 hours, 3 times/week for 3 weeks. After a 2-week rest period, the subjects were challenged at a naïve site. Only one person demonstrated irritation, expressed as slight erythema, occurring on at least 4 occasions out of 9 exposures. This same individual exhibited a delayed reaction at challenge to DEHT. Another individual, who did not show signs of irritation in the initial patch test, did exhibit a reaction at 48 hours after challenge. David et al. (2003) concluded that DEHT is non-irritating and non-sensitizing to humans.

A dermal sensitization Human Repeat Insult Patch Test (HRIPT) study (modified Draize method) was conducted using nine human volunteers of each sex (18 total) (Lockhart, 2001b). Subjects were exposed to nine repeated dermal applications of 0.5% DEHT in acetone under semi-occlusive conditions over a three-week induction period. Following a two weeks period without exposure, subjects were challenge with a 0.5% dose applied to the skin. DEHT appeared to be non-irritating and non-sensitizing in all volunteers.

Skin irritation to DEHT was evaluated in a GLP compliant study conducted according to the OECD guideline 404. In this study, 0.5 ml of undiluted DEHT was dermally applied to male and female New Zealand white rabbits (2 male/1 female) under occlusive conditions for 4 hours.

Following a 72 hour observational period, no erythema or edema were observed; therefore, DEHT was reported as non-irritating under the tested conditions (Product Safety Laboratories, 2006a; as cited by Ball et al., 2012; ANSES, 2015).

A non-GLP compliant dermal sensitization study was conducted using guinea pigs (strain/sex not reported, n = 5). Groups of guinea pigs were administered a 1% solution of DEHT (purity not reported) via injection into the footpad followed by a 1% dermal application challenge dose. No signs of sensitization were observed and DEHT was reported as non-sensitizing under the tested conditions (ToxServices, 2012; ANSES, 2015). However, ANSES (2015) considered this study to be of low reliability, due to the limited reporting.

As noted above in Section 5.1.2, Eastman Kodak Co. (1975, as reported by Versar, 2010; Ball et al., 2012) conducted a study in which male guinea pigs were exposed to 4920, 9840 or 19,680 mg/kg under occluded conditions for 24 hours, followed by a 14-day observation period. This study deviated substantially from currently-accepted guidelines, and included only one animal per dose. Edema was noted at all doses after 24 hours. Undiluted DEHT was reported to be slightly irritating to the skin for 24 hours and moderately irritating with repeated skin contact for 10 days (Eastman Kodak Co., 1975).

DEHT was reported to act as a sensitizer in guinea pigs, producing a strong skin sensitization reaction in 2/10 guinea pigs tested and a weak reaction in 6/10 guinea pigs (Eastman Kodak Co., 1975). However, current guidelines specify that animals should be exposed for 4 hours (not for 24 hours), that there should be at least 3 animals/dose (this study had only one animal/dose) and the maximal dose on exposure site should be 0.5 g (this study used 5-20 g). For these reasons the reliability for this study is low (ANSES, 2015); it is also likely that the observed response was related to the excessively stringent testing conditions.

Overall, DEHT is considered non-sensitizing.

DEHT (0.1 mL) was instilled into the eyes of 6 albino rabbits for about a minute and a half, after which time the treated eyes of 3 of the rabbits were washed with distilled water (Eastman Kodak Co., 1975, as cited by Versar, 2010). Slight erythema was observed one hour after treatment, in both washed and unwashed eyes. Twenty-four hours after treatment, this slight irritation was no longer observed and no other effects were seen during the 14-day observation period.

In a GLP and OECD 405-compliant eye irritation/corrosion study, DEHT was instilled into one eye of male and female New Zealand white rabbits (1 male/2 females). Rabbits were administered undiluted DEHT in one eye for a 4-hour exposure, followed by a 72 hour observational period. The study reported that no corneal opacity or iritis was observed. Conjunctivitis and redness were reported for a period of up to 48 hours post administration. Animals fully recovered from all reported effects within 72 hours of dose administration. Based

on these findings DEHT was not considered to be an eye irritant (ECHA, 2012, as cited by ANSES, 2015; ToxServices, 2012).

Teehaar (1975, as cited by ANSES, 2015) conducted a non-GLP compliant eye irritation/corrosion study using New Zealand white rabbits (n=6, sex not reported). The rabbits were exposed to undiluted DEHT in one eye. At 24 hours post administration one rabbit showed adnexal staining of the nictitating membrane. By 48 hours following exposure, all animals had recovered and appeared normal. ANSES (2015) concluded that classification as an eye irritant DEHT is not warranted since all effects were reversible within a 48-hour time period.

5.2 Repeated Dose Toxicity

5.2.1 Oral Toxicity

In a short-term study, groups of 5 male albino rats were administered DEHT at concentrations of 0, 0.1 or 1.0% (approximately 0, 85, 885 mg/kg-day; ANSES, 2015) in the diet 5 days/week for 2 weeks (Eastman Kodak Co., 1975, as cited by Eastman Chemical, 2010; ANSES, 2015; Ball et al., 2012). No significant changes were observed based on body weight, hematology, serum chemistry, or organ weights. Microscopic findings indicated that 2/5 high-dose rats had tracheitis and bronchiolitis, and 1/5 high-dose rat also exhibited hemorrhage beneath the hepatic capsule just before sacrifice. One control animal also demonstrated tracheitis, another demonstrated bronchiolitis, and two demonstrated interstitial pneumonia, suggesting possible infection among test animals. Therefore, although no treatment-related effects were observed in this study among rats fed a diet containing up to 885 mg/kg-day DEHT, possible infection among test animals limits the interpretation of these results.

In a published short-term feeding study, Sprague-Dawley rats (5/sex/dose) were administered DEHT at 0, 0.1, 0.5, 1.0, 1.2, or 2.5% continuously in the diet for 21 days (Topping et al., 1987). Based on U.S. EPA (1988) reference values for body weight and food consumption of Sprague-Dawley rats, the estimated doses are 0, 86, 431, 861, 1033 and 2154 mg/kg-day for males and 0, 98, 490, 980, 1176 and 2450 mg/kg-day for females. Body weight gain was significantly reduced in both sexes (by 40% M, 35% F, compared to controls) in high-dose animals ($p<0.001$). Feed consumption among rats fed DEHT in the diet at 1.2% was initially reduced compared to controls (first 3 days for males and first 10 days for females), but was statistically similar to controls for the remainder of the study, and body weight gain was similar to controls in this group. Feed consumption by male and female rats administered diets containing 2.5% DEHT was markedly reduced compared to controls over the entire study. The explanation provided was aversion to unpalatable diet containing high concentrations of DEHT. The reduced feed consumption resulted in a reduced actual daily DEHT dose, which was only 40% greater in the animals administered 2.5% diet than in the 1.2% group. The study authors attributed at least some of the effects seen in the high-dose rats to decreased food consumption, since the

magnitude of the difference in response between the 2.5% and 1.2% groups was larger than the difference in actual dose.

Relative liver weights were significantly elevated ($p<0.001$) over controls among high-dose rats of both sexes. Absolute liver weights in these rats were not significantly different from controls, indicating that the increases in relative liver weights were likely related to the reductions in body weight gain among high-dose rats. In addition, slight increases in liver weight are considered adaptive in the absence of additional indications of liver toxicity (U.S. EPA, 2002). Relative liver weights among female rats fed diets containing 1.0 or 1.2% DEHT were also significantly elevated over controls ($p<0.01$), but to a lesser degree than among high-dose (2.5%) females. Serum triglyceride levels among high-dose males were significantly ($p<0.01$) elevated over controls at the end of the 21-day study. However, triglyceride levels were lower than in males fed 0.5, 1 or 1.2% DEHT (but the higher triglyceride levels in the intermediate dose groups were not statistically significant), and were not found useful in interpreting the effects of DEHT. High-dose females also exhibited significant ($p<0.05$) increases in serum triglycerides over controls, but the difference in females was slight compared to the difference observed in males. Serum cholesterol levels were slightly but significantly ($p<0.01$ for males $p<0.001$ for females) elevated in high-dose animals over controls (2.1 vs. 1.8 mmol/L in males; 2.7 vs. 2.2 mmol/L in females). Topping et al. (1987) considered the triglyceride and cholesterol data of limited value because of the unclear dose-response in males that clearly differed from females for triglyceride levels and the relative lack of effect on cholesterol levels. High-dose animals also exhibited increases in liver enzymes and peroxisomes. However, Topping et al. (1987) concluded that since DEHT in the diet only caused liver effects at a level that severely decreased food consumption and weight gain, the findings based on liver enzymes and peroxisomes in high-dose animals are of doubtful significance, since fasting alone has been implicated in altered lipid metabolism and the formation of hepatic peroxisomes (Ishii et al., 1980, as cited by Topping et al., 1987). Based on these findings, a NOAEL of 1.2% in diet (1033 mg/kg-day for males and 1176 mg/kg-day for females) and a LOAEL of 2.5% (2154 mg/kg-day for males and 2450 mg/kg-day for females) are identified, based on decreased body weight gain and feed consumption, although at least some of the decreased weight gain is likely due to taste aversion.

In a GLP-compliant subchronic 90-day feeding study, DEHT (~99% purity) was administered continuously at concentrations of 0, 0.1, 0.5, or 1.0% in the diet to groups of 20 male and female Sprague-Dawley rats (Barber and Topping, 1995). Corresponding doses reported by the researchers were 0, 54, 277 and 561 mg/kg-day for males and 0, 61, 309 and 617 mg/kg-day for females. No mortality was observed and no significant changes occurred in mean feed consumption or body weight gain in either sex during the 90-day feeding study. Relative liver weights of high-dose animals were significantly ($p\leq0.05$) increased over controls by 11 and 9% in males and females, respectively. Absolute liver weights were also increased in these animals, but the differences did not achieve statistical significance (9 and 7% in males and females, respectively). None of the other organs weighed were significantly different from controls.

Slight changes (<5% difference from controls) in hematology were observed in mid- and high-dose animals. In particular, hemoglobin concentration, hematocrit, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were statistically significantly ($p \leq 0.05$) decreased from controls among high-dose males. MCH was also statistically significantly ($p \leq 0.05$) decreased among mid-dose males. Statistically significant ($p \leq 0.05$) decreases in MCV and MCH were also observed in mid- and high-dose females. No other dose-related changes in hematology were observed. Barber and Topping (1995) determined that in the absence of any other indications of anemia, the changes seen in the mid-dose rats were not considered to be biologically significant. No significant dose-related changes were observed based on serum chemistry.

Microscopic examination did not reveal any significant treatment-related abnormalities. DEHT did not induce hepatic peroxisomes among groups of five male rats from the control and treatment groups compared to rats treated with a positive control (2-ethylhexanol) at 1000 mg/kg-day, 5 days/week for 3 weeks. U.S. EPA (2002) noted that slight increases in liver weights in the absence of additional indications of liver toxicity are most likely indicative of an adaptive change and do not indicate an adverse effect. Therefore, for the purposes of this review, NOAELs of 561 mg/kg-day in males and 617 mg/kg-day in females are identified.

5.2.2 Inhalation Toxicity

Inhalation data for DEHT come from a short-term repeated-exposure study in which five male Sprague-Dawley rats were exposed to DEHT at 0 or 46.3 mg/m^3 for 8 hours/day, 5 days per week for 2 weeks (Eastman Kodak Co., 1983, as cited by Eastman Chemical, 2010; Versar, 2010). Exposure was reported to be "primarily as an aerosol." No significant effects were observed among rats based on hematology, serum chemistry or pathological examination at 46.3 mg/m^3. The lack of study details including a description of study design and procedures limits the interpretation of these results.

ANSES (2015) reported on a repeated-exposure study without citation, in which male albino rats (5/dose) were exposed to 0 or 0.0718 mg/L (71.8 mg/m^3) DEHT in air for 6 hours/day for 14 days. An extensive array of endpoints was evaluated, including body weight, clinical chemistry, hematology, and extensive histopathology. There was no mortality and only minor changes were observed in other endpoints. Therefore, a NOAEL of 71.8 mg/m^3 was identified.

5.2.3 Dermal Toxicity

Five Dunkin-Hartley guinea pigs were administered undiluted DEHT dermally at doses equivalent to 813 to 1144 mg/kg-day applied to the clipped skin once a day for 9 applications over an 11-day period. No mortality was observed and it was reported that no signs of skin absorption nor systemic toxicity were evident, although only clinical signs of toxicity and body weight gain were evaluated. There was no exacerbation of the irritant response following

repeated DEHT applications; moderate erythema was seen in one animal following the first application and severe erythema was seen in the other four guinea pigs. Slight edema was observed for all animals but this disappeared by study termination. Necrosis and eschar were not observed in this study (no citation provided for the primary study, as cited by ANSES, 2015; ECHA, 2012). ECHA (2012) concluded that DEHT is not acutely toxic following repeated dermal application but may cause moderate dermal irritation.

5.3 Chronic Toxicity/Carcinogenicity

A GLP compliant 104-week carcinogenicity and chronic toxicity study was conducted in accordance with EPA OPPTS 870.4200 guideline. In this study, male and female Fischer 344 rats (50/sex/dose) were allowed free access to diets containing DEHT (>98% purity) at 0, 1500, 6000 or 12,000 ppm for 104 weeks (Deyo, 2008). Average daily doses reported by Deyo (2008) were 0, 79, 324 and 666 mg/kg-day for males and 0, 102, 418 and 901 mg/kg-day for females. Survival rates at the end of the 2-year study were equivalent to that of control rats for all treatment groups; a dose-related increase in survival percentage was seen among female rats. Body weight gains among high-dose animals were significantly lower than controls during the course of the 2-year study. Mid-dose animals also demonstrated significant reductions in body weight gain compared to controls, but only during the first year of the study. Terminal body weights were significantly different (level not reported) from controls only among high-dose females. In contrast to observations in high dose animals dosed for 21 days (Topping et al., 1987), Deyo (2008) noted that food consumption and food conversion efficiency were not affected at any dose; this means that the decreased body weight could not be attributed to poor palatability. The author also noted that decreased body weight gains have been shown to enhance survivability of rats in chronic studies and suggested that this likely played a role in decreased mortality rates for females in this study.

Changes in hematology, clinical chemistry, and urinalysis were of minimal magnitude and biological significance, were confined to one sex in some cases, were often within historical controls levels and were not accompanied by additional histological evidence of adverse effects (Deyo, 2008). Therefore, Deyo (2008) attributed changes in hematology, clinical chemistry, and urinalysis to the normal biological variability associated with geriatric animals. However, while not adverse, the decreased urinary pH at the mid- and high-doses are of mechanistic interest. The decrease was statistically significant ($p<0.01$) and dose-related. Ball et al. (2012) noted that the DEHT metabolite TPA can decrease urinary pH, resulting in the production of urinary stones that are made of largely of calcium terephthalate, with or without calcium hydrogen phosphate (Chin et al., 1981, as cited by Ball et al., 2012). The small changes in urinary pH suggests that TPA may be causing some effect, but the concentration of TPA is not high enough to result in the formation of stones.

Absolute liver weights were not different from controls among any treatment group, but relative liver weights were significantly elevated among high-dose females compared to controls ($p < 0.01$). Relative liver weights among high-dose males were elevated in comparison to controls but did not reach a level of statistical significance. The only corresponding adverse histological finding in livers was an increase in the incidence of portal lymphoid foci among high-dose males surviving to study termination (15/26 vs. 8/29 controls; significant at $p<0.05$). However, livers from male rats also showed a trend for a decreased incidence of periportal vacuolization. Absolute kidney weights were significantly decreased from controls among high-dose males ($p < 0.01$) and mid- and high-dose females ($p < 0.01$). Relative kidney weights were significantly decreased from controls among low- and mid-dose males ($p < 0.01$) (but not high-dose males), and among mid-dose females ($p < 0.01$) (but were *increased* in high-dose females ($p < 0.05$). Histology did not reveal any significant increases in kidney lesions and instead showed a trend for a decreased incidence of chronic progressive nephropathy and mineralization of the pelvic/papillary epithelium. Aside from liver and kidney weights, organ weight changes that attained statistical significance were regarded by Deyo (2008) as either a result of high individual variability or as effects secondary to changes in body weight.

Additional histological findings included an increased incidence of eosinophilic inclusions in the nasal turbinates and atrophy of the outer nuclear layer (ONL) of the retina among both sexes (Deyo, 2008). Specifically, significant increases in lesions of the nasal turbinates occurred among all of the early decedent high-dose females (14/14 vs. 12/23 controls, $p < 0.01$) and among high-dose females surviving to study termination (33/36 vs. 17/27 controls, $p<0.05$). These lesions occurred despite careful control of cage rotation and light/dark sequencing. Deyo (2008) reported that these lesions were considered an exacerbation of an age-related finding and not of any toxicological significance. However, in the absence of other information, such exacerbation is considered adverse and relevant to humans.

Atrophy of the ONL occurred to some degree in all animals surviving to termination. The initial pathology evaluation concluded that atrophy of the ONL occurred in a dose-related incidence in female rats. However, a follow-up investigation by a pathology working group (PWG, also described by Deyo, 2008) found that this lesion occurred in essentially every rat of both sexes in the treated and control groups at study termination. Although the incidence was not increased among the DEHT-treated animals, severity of the lesion was significantly greater compared to controls among mid- and high-dose females ($p < 0.05$), and males in the high-dose group ($p <0.05$) (Table 2). Deyo (2008) stated that this change is a common degenerative change observed in geriatric albino rats, although the severity was exacerbated by DEHT exposure. The PWG also considered the changes to be consistent with photo-induced toxicity. Deyo (2008) concluded that higher doses of DEHT exacerbate retinal ONL degeneration (rather than being a primary inducer of the effect), and identified a NOAEL of 324 mg/kg-day for males and of 102 mg/kg-day for females for this endpoint; the corresponding LOAELs are 666 and 418 mg/kg-day, respectively. Because a detailed mode of action (MOA) evaluation has not been conducted, it is prudent and

health-protective to assume that this effect is potentially relevant to humans. However, because the observed effect was an exacerbation of a pre-existing condition, rather than the induction of a new lesion, it is also reasonable to expect that humans would be much less sensitive than rats. As noted, the lesion was observed in essentially every rat in the Deyo study, including controls. While the incidence in humans was not readily available, it is reasonable to expect that it would be much lower.

Table 2. Incidence of Lesions Among DEHT-Treated Rats[a]

Lesion	Dose (mg/kg-day)			
Males	**0**	**79**	**324**	**666**
ONL[d] atrophy (mean severity score, surviving to termination)	2.2	2.3	2.5	3.0[b]
Nasal turbinates –eosinophilic inclusions (terminal sacrifice)	7/29	0/0	0/0	13/26
Granular cell lymphomas	13/29	19/26[b]	16/29	8/26
Females	**0**	**102**	**418**	**901**
ONL atrophy (mean severity score, surviving to termination)	3.3	3.3	3.7[c]	3.9[c]
Nasal turbinates –eosinophilic inclusions	17/27	18/31	27/34	33/36[b]
Granular cell lymphomas	6/27	6/31	7/34	8/36

[a]Deyo (2008)
[b]Significantly different from control at $p<0.05$
[c]Significantly different from control at $p<0.01$
[d]Outer nuclear layer of the retina (ONL)

No significant differences were observed in the incidence of specific tumors between treated and control rats that died or were killed prior to study termination (data not shown) (Deyo, 2008). Among animals surviving to study termination, the only significant increase in tumor incidence was for large granular cell lymphomas in low-dose males. However, the incidence of this lesion decreased with increasing dose level as shown in Table 2 and is thus not considered to be related to treatment with DEHT.

In summary, it is concluded that ophthalmic ONL changes reported by Deyo (2008) are an adverse exacerbation of atrophy commonly observed in geriatric albino rats with NOAELs of NOAEL of 324 mg/kg-day for males and of 102 mg/kg-day for females. Because the underlying effect appears to be related to photo-toxicity in albino rats and exacerbation of a pre-existing condition, humans (except for those with albinism) are likely to be much less sensitive to this endpoint. The incidence of eosinophilic inclusion of the nasal turbinates were not significantly increased in males at any dose (either as those surviving to termination or total) but these lesions were increase for females with a NOAEL of 418 mg/kg-day and a LOAEL of 901 mg/kg-day. The increased relative liver weight in females was not considered adverse, in light of the absence

of liver lesions (NOAEL = 901 mg/kg-day in females), and the NOAEL for liver effects in males is 324 mg/kg-day, based on an increased incidence of portal lymphoid foci. It is unclear whether the kidney effects (decreased absolute weights in the absence of a dose-related change in relative weight or histopathology) are adverse.

An apparently separate combined toxicity and carcinogenicity study is described by the Danish EPA but without attribution (Danish EPA, 2010). DEHT was evaluated in a combined chronic toxicity and carcinogenicity study. DEHT was administered to male and female Fischer-344 rats in diets at doses of 20, 142, and 1000 mg/kg-day. The only treatment-related sign of toxicity reported was eye opacities (cataracts) that were "frequent" in all groups; no additional details on this lesion were available. Grossly, at 1000 mg/kg-day, body weights and female liver weights were reduced. There were no consistent reductions in food consumption. No treatment-related effects were evident from the gross and histopathologic examinations conducted at 6 and 12 months. At 18 months hyperplasia and/or transitional cell adenomas of the urinary bladder and adenomas or adenocarcinomas of the uterus "appear to be associated" with the 1000 mg/kg-day treatments in females. No additional details on this study have been identified, but the Danish EPA (2010) considered DEHT "negative" for carcinogenicity.

5.4 Reproductive Toxicity

In a two-generation reproductive toxicity study (OECD Guideline 416), Sprague-Dawley rats (30/sex/dose) were administered DEHT (purity >97%) continuously in the diet at target concentrations of 0, 0.3, 0.6 or 1.0% (Faber et al., 2007b). Males were exposed for at least 70 days prior to and during mating, and females were exposed for at least 70 days prior to mating, during mating and through gestation and lactation. Male and female pups from the F1 generation from each litter were exposed under similar conditions beginning on postnatal day (PND) 22. Average doses for F0 animals based on the mean calculated compound consumption for various periods during the study as reported by Faber et al. (2007b) were 0, 158, 316, and 530 mg/kg-day for males and 0, 273, 545, and 868 mg/kg-day for females. Similarly, average doses for F1 animals were 0, 208, 422 and 723 mg/kg-day for males and 0, 306, 630 and 1034 mg/kg-day for females. Reproductive parameters evaluated in this study included mating and fertility indices, estrous cycle lengths, pre-coital intervals, gestation lengths, gender ratios, live litter size, and postnatal survival. No adverse effects on reproduction were observed in either generation at any dose level. In addition, no significant changes in sperm concentration, motility, or morphology were observed and no significant histological findings in males were reported. Thus, a reproductive NOAEL of 1.0% (530 mg/kg-day for the F0 males, 723 mg/kg-day for the F1 males, 868 mg/kg-day for the F0 females and 1034 mg/kg-day for F1 females) was established by the study authors (ANSES, 2015).

Faber et al. (2007b) reported indications of systemic toxicity in both growing pups and adult animals. Among high-dose females, 3 F0 dams and 7 F1 dams died or were euthanized in

extremis 2 to 8 days after weaning of the pups (Faber et al., 2007b). Pathology did not indicate a cause of death in these dams, but the authors stated that the unusual timing of mortality suggests that these deaths were related to treatment with DEHT (Faber et al., 2007b). Single male deaths *not* considered to be related to treatment by Faber et al. (2007b) occurred in the F0 control and mid-dose groups and in the F1 high-dose group. High-dose males of the F0 generation demonstrated significant reductions in mean weekly body weight gain (15-25%) during weeks 3 through 7, which resulted in a slight reduction (5%) in mean terminal body weights. Mid- and high-dose F1 males demonstrated lower mean birth weights compared to controls, and decreased growth before weaning resulting in reduced mean body weights throughout the generation. Feed consumption in these male rats was also slightly reduced (10%) during the first week after weaning for the mid-dose group and throughout the generation for the high-dose group, suggesting that taste aversion was the reason for the decreased body weight, at least at the high dose. A NOAEL of 0.3% (about 150-200 mg/kg-day) for male parental toxicity has also been derived based on the effects on the body weight (ANSES, 2015).

The rate of maternal body weight gain through gestation, feed consumption, and mean maternal body weights on gestation day (GD) 20 and throughout lactation were significantly reduced in the high-dose F0 dams. Similar effects were observed among the high-dose F1 dams, although the reductions in mean maternal body weights were found throughout gestation and were of greater severity than that observed in the F0 dams. Mean body weights and feed consumption among mid-dose F1 dams were also significantly reduced during lactation days 7-14. Reductions in postnatal pup body weights occurred at concentrations corresponding to reduced feed consumption among mid- and high-dose dams, indicating a possible secondary effect. The study authors noted that it was not possible to distinguish whether the decreased pup weight was due to taste aversion (from pup consumption of feed), an indirect effect mediated through decreased lactation capacity of the dam, or a direct toxic effect of DEHT, although they suggested that the observation of pup weight decreases on PND 4-7 indicated that at least part of the effect was mediated through lactation.

Significant increases were observed in absolute (F0) and mean relative liver weights (both generations) among the mid- and high-dose females. However, no morphological changes indicative of liver damage were observed in either generation, indicating that the observed increases in liver weights were most likely adaptive changes rather than adverse effects.

No macroscopic findings attributable to exposure to DEHT were noted at the scheduled necropsy of F1 and F2 pups euthanized on PND 21 (Faber et al., 2007b). Treatment-related effects in F1 and F2 pups included reduced mean relative spleen weight in the high-dose F1 males (13%) and the high-dose F2 males (8%) and females (11%), reduced mean relative thymus weight in the high-dose F2 females (12%), and increased mean relative brain weights for both sexes in the high-dose F1 (25%) and F2 (23-25%) pups and the mid-dose F1 females (12%). These changes were not related to decrements in pup body weight.

There was no effect on the mean age of attainment of vaginal patency F1 females. In F1 males, there was no effect on the mean age of attainment of balanopreputial separation in the two lower dose groups, but a significant ($p<0.05$) delay was seen at the high dose. The authors considered the delay to be secondary to the decreased pup body weight, noting that body weight decrements delay the onset of puberty in rats. In addition, the percent increase in age of balanopreputial separation was comparable to the percent decrease in pup mean body weight, and the delayed age was within the historical control range. Thus, the study authors concluded that there was no adverse effect on the age of attaining developmental landmarks.

Overall, based on the findings described above, this study identified a NOAEL of 530 mg/kg-day (males) and 868 mg/kg-day (females) for reproductive toxicity, and a NOAEL of 158 mg/kg-day (males) and 273 mg/kg-day (females) for parental and pup systemic toxicity. There was no evidence of developmental effects other than decreased pup weight, which may or may not have reflected direct DEHT toxicity.

Two additional studies have been conducted in rats to evaluate the effect of DEHT on estrogenic activity in immature female rats (Faber et al., 2007a) and to evaluate the effects of DEHT on the male reproductive tract after perinatal exposure (Gray et al., 2000). One study, Faber et al. (2007a), performed a uterotrophic assay for evaluating estrogenic activity in rats by administering DEHT (purity >97%) to groups of 10 immature female Sprague-Dawley rats at 0, 20, 200 or 2000 mg/kg-day in corn oil by gavage daily on PND 19-21. In this study, an additional group of 10 immature female rats received 0.003 mg/kg-day 17α-ethinyl estradiol (EE) as a positive control under similar treatment conditions. No mortality, clinical signs or differences in mean body weights were observed. However, mean body weight gain in the high-dose group was reduced after the first day of dosing, which resulted in a 19% reduction in mean body weight gain over the entire treatment period. No significant differences were observed in mean wet and blotted uterine weights or in the corresponding mean luminal fluid weight. The positive control group had increased uterine weights as expected. Faber et al. (2000a) identified a NOAEL of 2000 mg/kg-day for estrogenic activity in rats.

The second study conducted in rats to investigate estrogenic activity (Gray et al., 2000), administered DEHT (purity 98%) by gavage to groups of 8 pregnant Sprague-Dawley rats at 0 or 750 mg/kg-day in corn oil during the period of sexual differentiation in pups from GD 14 to PND 3. No mortality or significant changes in maternal body weights was observed among treated dams, and the number of live pups at birth was not affected by DEHT treatment. In addition, there were no significant reductions in mean pup weights at birth. Male offspring were examined for signs of demasculinization (e.g., altered anogenital distance, testis weight, nipple retention) and male reproductive tract malformations, but no effects were seen at 750 mg/kg-day. A slight decrease in serum testosterone was reported, but this change did not reach statistical significance (ToxServices, 2012). Gray et al. (2000) concluded that DEHT does not produce antiandrogenic effects in rats. Liu et al. (2005, as cited by Ball et al., 2012) found no significant

effect on testicular gene expression in pups exposed to DEHT in utero, unlike the tested phthalate esters.

ToxServices (2012), in their 2012 Green Screen report, noted an absence of effects on reproductive organ weights in both the Gray et al. (2012) study and the Faber et al. (2007b) 2-generation study, together with the absence of spermatogenic parameters in the 2-generation rat study. ToxServices (2012) concluded that DEHT is unlikely to affect the endocrine activity in male rats. Furthermore, DEHT is unlikely to affect endocrine activity in female rats, based on the absence of estrogenic effects on developmental toxicity and uterotrophic assay. Based on the available data, ToxServices concluded that there was no evidence of endocrine activity for DEHT in the available studies (ToxServices, 2012).

5.5 Prenatal, Perinatal, and Postnatal Toxicity

In a developmental toxicity study in Sprague-Dawley rats conducted by the same researchers who performed the two-generation reproduction toxicity study, DEHT (purity >97%) was fed to groups of 25 pregnant rats at 0, 0.3, 0.6 or 1.0% from GD 0-20 (Faber et al., 2007a). Corresponding doses reported by the researchers were 0, 226, 458 and 747 mg/kg-day. No effects were observed on feed consumption. A significant reduction in maternal body weight gain (10%) was observed among high-dose rats during GD 16-20 compared to the controls. However, mean maternal body weights were comparable to the control group throughout the entire treatment period. Significant reductions were also observed in the net body weights (5%) and net body weight gains (25%) of the high-dose rats. Gravid uterine weights in this group were statistically similar to controls. These findings indicate that body weight changes are primarily maternal effects and not intrauterine. Significant increases in mean absolute liver weights (8%) were observed among high-dose rats. Relative liver weights were not reported, but based on the terminal body weights they would be elevated in high-dose rats over controls. The magnitude of this change in liver weight is considered adaptive in the absence of liver histopathology. This study identified a maternal LOAEL of 747 mg/kg-day and NOAEL of 458 mg/kg-day based on the reductions in mean and net maternal body weight gains.

Fetal growth and survival were unaffected by DEHT treatment at any dose level (Faber et al., 2007a). No differences in the overall total number of skeletal variations were observed between treatment groups and controls. However, there was an increase in the number of fetuses with 14th rudimentary ribs in the high-dose group. When evaluated on a litter basis, this increase was significant (13.3% incidence in the high-dose group versus 5.1% among controls). Faber et al. (2007a) reported that the incidence of rudimentary 14th ribs among fetuses from the high-dose group was only slightly increased when compared to the range of values based on historical controls (2.11-12.01%). Faber et al. (2007a) also stated that rudimentary 14th ribs represent the most common skeletal developmental variation in laboratory rats and noted that this variation has been shown to represent transient changes that do not persist into adulthood. Faber et al.

(2007a) identified a NOAEL of 747 mg/kg-day for developmental toxicity. However, since the incidence of rudimentary 14th ribs did exhibit a dose-related increase and was both statistically significantly elevated in the high-dose group compared to concurrent controls, when evaluated on a per litter basis, and elevated above the range of historical controls, this effect is considered a possible indication of developmental toxicity in this study. Therefore, for the purposes of this review, a NOAEL of 458 mg/kg-day is identified for developmental toxicity.

In a second developmental study in ICR mice, DEHT (purity >97%) was fed to groups of 25 pregnant mice at 0, 0.1, 0.3 or 0.7% from GD 0-18 (Faber et al., 2007a). Corresponding doses reported by the researchers were 0, 197, 592 and 1382 mg/kg-day. These doses were based on an unpublished dietary range-finding study (Knapp, 2005). No effects were observed on mean maternal body weights or body weight gains, or on feed consumption. No treatment-related effects were observed on net body weights (i.e., body weight exclusive of uterus and contents), net body weight gains or gravid uterine weights compared to controls. Increased absolute liver weights were noted in the mid- (8%) and high-dose (15%) mice compared to controls. The study authors did not consider the increased liver weight in the mid-dose mice to be treatment-related, since it was comparable to a mean control group value obtained in the range-finding study by Knapp (2005). However, comparison to concurrent control is more important than comparison to a historic control, and there was an apparent dose-response trend, and so this assessment considers the increased liver weight at the mid-dose to be treatment-related. Relative liver weights were not reported, but based on the terminal body weights it appears that they were elevated in mid- and high-dose mice over controls. Mean litter proportion of preimplantation loss in the mid-dose group was significantly higher compared to the controls (6.7% versus 3.0%). However, since this effect was not observed in the high-dose group, it was considered by Faber et al. (2007a) to not be related to DEHT treatment. Overall, intrauterine growth and survival were unaffected by DEHT treatment at any dose level. Six fetuses in 2 litters of the mid-dose group exhibited tarsal flexure or cleft palate. Faber et al. (2007a) did not consider these external malformations to be treatment related, as they were clustered primarily in one litter and no corresponding malformations were observed in the high-dose group. Visceral developmental variations noted in single fetuses in the mid- and high-dose groups were similar to controls when evaluated on a litter proportional basis. Therefore, no significant malformations or variations were attributed to treatment with DEHT in mice in this study. Faber et al. (2007a) identified a NOAEL of 197 mg/kg-day for maternal toxicity based on increased liver weights and a NOAEL of 1382 mg/kg-day for developmental toxicity. No other evaluations of potential liver damage in these mice were conducted by Faber et al. (2007a). It is theoretically possible that the dams had lesions in the liver, since no liver histopathology evaluation was conducted in this study. However, the absence of liver lesions in any other study of DEHT, including in a chronic rat study at doses up to 666 mg/kg-day (Deyo, 2008) and a 2-generation reproductive toxicity study at doses up to 723 mg/kg-day for males and and 1034 mg/kg-day for females (Faber et al., 2007b) supports the conclusion that DEHT causes enzyme induction and associated increased liver weight, but not overt liver damage. These studies did not doses quite as high as in the

developmental study, but pregnant dams were exposed, and the overall exposure duration was longer. Thus the enlarged livers are likely adaptive changes to DEHT treatment rather than adverse effects (U.S. EPA, 2002). For the purposes of this review, a NOAEL of 1382 mg/kg-day is identified for maternal toxicity.

5.6 Genotoxicity

Limited data suggest that DEHT is not genotoxic. A single study has shown that DEHT did not induce reverse mutations in various strains of *Salmonella typhimurium* (non-GLP), forward mutations at the HGPRT locus of Chinese hamster ovary (CHO) cells (similar to OECD 476), or chromosome aberrations an OECD 473-similar chromosomal aberration assay in CHO cells (Barber, 1994, as cited by ToxServices, 2012). All of these studies were conducted both with and without exogenous metabolic activation. In addition, urine from rats fed DEHT in the diet at 2000 mg/kg-day for 15 days did not induce mutagenic activity with or without metabolic activation in various strains of *Salmonella typhimurium* (Divincenzo et al., 1985 as cited by Eastman Chemical Co., 2010).

5.7 Mechanistic/Mode of Action Studies

Only a limited number of mechanistic/mode of action studies have been conducted.

DEHT is a structural isomer of the phthalate DEHP, which is a well-recognized teratogen and endocrine disruptor. A detailed evaluation of the structures of DEHT and DEHP and resulting differences in metabolism aids in understanding the reason for the marked difference in the toxicity of DEHT and DEHP, despite their structure similarity. Although these two compounds have qualitative structural similarity, DEHT is the benzene-1,4-dicarboxylic acid (terephthalic acid = *para position)*, while DEHP is a benzene-1,2-dicarboxylic acid (phthalic acid = *ortho position*). This *para vs. ortho* structural difference is critically important for the difference in metabolism and subsequent toxicological effects that distinguish DEHP from DEHT (Wirnitzer et al., 2011). It appears that the para structure of DEHT permits complete hydrolysis, yielding 2 molar equivalents of 2-ethylhexanol (2-EH) per equivalent of TPA, and these metabolites are rapidly excreted (Barber et al., 1994). In support of this conclusion, two other terephthalic esters, di-methylterephthalate (DMT) and di-butylterephthalate, which also possess this *ortho* positioning, are likewise known to undergo rapid and complete hydrolysis (Kamendulis et al., 2002). By comparison, DEHP does not undergo such metabolism; rather, it is metabolized by intestinal lipases (and to a lesser extent other tissues) to mono(2-ethylhexyl) phthalate (MEHP). MEHP appears to be the active species responsible for the observed toxicities of DEHP (Rettenmeier and Mettang, 1997, as cited by Wirnitzer et al., 2011). The rapid and extensive hydrolysis of DEHT to TPA and 2-EH and MEHT permits a very low yield of mono(2-ethylhexyl) phthalate (MEHP), which limits the potential for MEHP-associated toxicological effects (Ball et al, 2012; SCENIHR, 2008).

Eljezi et al. (2016) investigated the cytotoxicity of a range of phthalates and their metabolites. In this *in vitro* study, murine fibroblast L929 cells were exposed to each phthalate and synthesized metabolites at concentrations of 0.01, 0.05 or 0.1 mg/mL. Cytotoxicity was quantified using cellular reduction of the colorimetric MTT reagent relative to positive and negative controls. DEHT demonstrated no significant differences compared with DMSO at any of the three concentrations tested. The only metabolite of DEHT evaluated was MEHT. At a concentration of 0.05 mg/mL, MEHT was as toxic as MEHP, a primary metabolite of DEHP. At 0.1 mg/mL, MEHT was as toxic as DEHP, and more toxic than MEHP. Across all the phthalates and metabolites tested, it was a general trend that metabolism of plasticizers increased their cytotoxicity. Metabolism of DEHT is relatively low; MEHT and other metabolites account for no more than about 9.3 % of an administered oral dose of DEHT. This suggests that cytotoxic effects of DEHT may be due to the toxicity of the MEHT metabolite, rather than that of the parent compound.

5.8 Mode of Action

Unlike other phthalic acid esters that have received significant toxicological scrutiny, DEHT has not been found to have adverse effects in reproductive organs, or kidneys. Effects observed in the liver were limited to increased liver weight (unaccompanied by liver pathology or clinical chemistry indications of liver damage where it was evaluated), and weak induction of peroxisomes (possibly secondary to decreased food consumption, as noted by Topping et al., 1987). In addition, an increased incidence of rudimentary 14^{th} ribs has been reported (Faber et al., 2007a), although the adversity of these changes is unclear. Repeated-dose studies, including a 2-year chronic rat study and a multigeneration reproduction study, demonstrated no hematotoxic and immunotoxic effects or histopathological lesions of the liver, thyroid or reproductive system. Furthermore, in human studies (Lockhart, 2001b; David et al., 2003), dermal application of DEHT did not induce any adverse skin reaction.

The clearly lower toxicity of DEHT, as compared to DEHP, has been considered to be based on the distinct pharmacokinetic differences between these compounds. As described by Barber et al. (1994), relatively little of the orally administered DEHT is absorbed as the parent compound. Instead, DEHT is hydrolyzed in the intestines to terephthalic acid (TPA) and 2-ethylhexanol (EH) with rapid excretion of both (SCENIHR, 2008). This extensive hydrolysis of DEHT to TPA and EH allows only a small fraction to be converted to mono(2-ethylhexyl) phthalate (MEHP). By contrast, DEHP is primarily metabolized in the intestines (and to a lesser extent other tissues including the liver, lungs and kidneys) to MEHP, which is considered to be responsible for the observed toxicities (Rettenmeier and Mettang, 1997). Wirnitzer et al. (2011) administered DEHT by intravenous (iv) infusion to male and female Wistar rats at doses of 38.2, 114.5 or 381.6 mg /kg-day over a period of 12 hours for 28 days. The authors reported no DEHT-related effects on any evaluated parameters, including gross animal appearance/behavior, survival, body weight, organ weights, blood chemistry, hematology, urinalysis (with exception of decreased pH) or food

and water consumption at any dose level. Exposure to DEHT did not impact hepatic function, liver weight, histopathology, enzyme activity, or triglyceride concentration. Due to the relatively low gastrointestinal absorption of DEHT, it is inferred that intravenous infusion results in systemic DEHT exposures much greater than oral exposures at similar applied doses. Thus, the data of Wirnitzer et al. (2011) suggest that the effects of DEHT observed in feeding studies are not attributable to DEHT itself, but instead are due to the metabolites formed from hydrolysis in the intestine. Since the doses administered in this study are in the range of the NOAELs identified in subchronic and chronic studies for body weight changes and increased relative liver weight, it is possible that higher doses, which would have resulted in greater exposure to metabolites, might have had these effects in the iv study.

Thus, based on this analysis, it is proposed that the observed effects of DEHT are due to its metabolites. However, beyond this distinction of the active form, further elucidation of the MOA, including identification of key events is not possible with the current data set.

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

The available toxicity studies consistently show that DEHT reduces body weight/body weight gain, although following high-dose exposures, this decrease may be due to poor feed palatability. Liver weight was also increased in many studies. Increases were accompanied by minimal or no peroxisome proliferation, although portal lymphoid foci were seen in one study. Other observed effects included an increase in the severity of retinal ONL degeneration, increased kidney weight, decreased fetal body weight (potentially secondary to decreased maternal weight gain), and increased skeletal variations. Individual studies have noted sporadic effects on clinical chemistry (serum cholesterol, triglycerides), hematology (MCV, MCH, hematocrit) and histopathology that were not considered toxicologically significant. In studies conducted to evaluate endocrine effects, no effects on androgenic or estrogenic endpoints were observed.

Decreased absolute body weight and/or body weight gain are consistent findings in repeated-dose rat studies at high doses. At least in the short-term, high-dose studies, the decreased weight appears to be due to decreased consumption of unpalatable high-dose DEHT feed. Decreases of final body weight as large as 40% were seen in rats treated with feed containing 2.5% DEHT (final dose 2154 mg/kg-day) for 21 days (Topping et al., 1987), and were also significant at 1.2% in feed. The hypothesis of poor palatability is consistent with the decrease at early time points of this study followed by normalization of intake, although this phenomenon could also reflect adaptation. There was no effect on body weight or feed consumption in rats administered doses up to 1% in feed for 90 days (Barber and Topping, 1995). However, decreased body weight was reported in the absence of an effect on feed consumption in a 2-year bioassay with rats fed 12,000 ppm DEHT in feed (666 mg/kg-day males, 901 mg/kg-day females; Deyo, 2008). Decreased mean maternal body weight, accompanied by decreased food consumption, was also

reported in the 2-generation study at 0.6% and 1.0% in feed, and in the rat developmental study at 1.0%, but not in the mouse developmental study (Faber et al., 2007a).

The primary consistent effect on the liver was increased liver weights. In some cases, only increases in relative liver weight were observed, in the absence of an increase in absolute weight. For example, in the 21-day feeding study (Topping, 1987), increased relative weight was seen in males at 2.5%, and in females provided feed with 1.0% or 1.2% DEHT. Although the increase may have been secondary to decreased body weight at the high dose, no decrease in terminal body weight was reported at 1.0% or 1.2%. In the subchronic rat feeding study (Barber and Topping, 1995), relative liver weight in males and females was significantly increased at 1% in feed, and absolute liver weight was increased by a smaller degree that was not statistically significant. In the chronic rat feeding study (Deyo, 2008), there was no effect on absolute liver weight but relative liver weight was increased at the high dose (901 mg/kg-day, significantly in females; 666 mg/kg-day, not statistically significant in males). Increased liver weight in exposed dams was also seen in the developmental studies in rats and mice (Faber et al., 2007a), and in the 2-generation study (Faber et al., 2007b). These changes in liver weight were considered adaptive, reflecting enzyme induction, when not accompanied by other liver changes. Although the developmental studies did not conduct histopathology or clinical chemistry evaluations, the absence of liver damage in other studies at longer durations (and somewhat lower doses) supports the supposition that liver damage did not occur in developmental toxicity study. It is noteworthy that none of these studies reported liver hypertrophy, hyperplasia, or inflammation.

Centrilobular peroxisome proliferation has only been reported by Topping et al. (1987) and was limited to only the highest tested dietary concentration (2.5%). No effect was observed at the 1.2% treatment level and below, and no peroxisome induction was observed in any other study available for review. In the Topping et al. study, the magnitude of peroxisome induction was reported as slight for both male and female rats, and was considered potentially secondary to the marked decrease in food consumption at the high dose. The only other histopathological change was an increased incidence of portal lymphoid foci in male rats treated chronically with dietary DEHT at a dose of 666 mg/kg-day; there was no effect in this study on serum markers of liver damage (Deyo, 2008).

Decreased absolute kidney weights were observed in rats treated chronically with dietary DEHT at a dose of 666 mg/kg-day (males) or 901 mg/kg-day (females), but there was no effect on relative kidney weight at this dose (Deyo, 2008). In addition, there was no histological evidence of kidney damage, and none of the other systemic toxicity studies reported any effects on the kidney. Therefore, the toxicological significance of this change is unclear.

Two histopathological findings were observed in the chronic study (Deyo, 2008). Increased severity of retinal ONL degeneration (loss of the outer nuclear layer of the retina) was seen in both sexes at the high dose of 666 mg/kg-day (males) or 901 mg/kg-day (females). This effect

was considered to be an exacerbation of an effect common to geriatric albino rats, and was considered to be evidence of photo-induced toxicity, an effect to which albino rats are particularly susceptible. Although a detailed MOA is not available for this endpoint, it is reasonable to expect that humans are not susceptible to photo-induced lesions in the eye from normal indoor lighting. Therefore, it is likely that humans (except perhaps those with albinism) are much less susceptible than rats to this endpoint.

Ball et al. (2012) derived an RfD based on the ocular lesion. They calculated a $BMDL_{10}$ of 54 mg/kg-day and applied a total uncertainty factor of 300 (10 for interspecies differences, 10 for human variability, and 3 for lack of a systemic toxicity study in a second species), resulting in an RfD of 0.2 mg/kg-day (rounded). However, this BMDL is based on incidence data. As noted, the PWG determined that the ocular lesion was found in all rats, but the severity increased with DEHT exposure. This raises questions about the appropriateness of this RfD, in addition to the noted higher sensitivity of albino rats to this photo-toxicity-related endpoint.

Ball et al. (2012) also calculated an alternative RfD of 2 mg/kg-day, based on the human urinary concentration of TPA that would produce bladder calculi.

Deyo (2008) also reported increased eosinophilic inclusions of the nasal turbinates among high dose (901 mg/kg-day) females, but not in males. Although Deyo (2008) considered these lesions to be an exacerbation of an age-related finding and not of any toxicological significance, this assessment considered them adverse and potentially relevant to humans, in the absence of other information.

DEHT is not a reproductive toxin. In the two generation rat feeding study (Faber et al., 2007b), no reproductive effect was observed at any dietary concentration (up to 1.0% w/w) for either the F0 (parent) or F1 (off spring) generation. F1 and F2 mean live liter sizes, numbers of pups born, percentages of males per litter at birth and sperm parameters were unaffected by treatment at any concentrations. Additionally, no uterotropic effects were seen in the offspring of rats gavage dosed with up to 2000 mg/kg-day on PND 19-21 (Faber et al., 2007a) and there was no evidence of demasculinization in the male offspring of rats gavage dosed with 750 mg/kg-day on GD 14 – PND 3 (Gray et al., 2000). There was no effect on male or female reproductive organs in the subchronic (Barber and Topping, 1995) or chronic (Deyo, 2008) studies.

The developmental toxicity of DEHT is low. In the 2-generation study (Faber et al., 2007b), the only developmental effect was decreased pup weight at 0.6% and higher, an effect that may have been secondary to decreased maternal body weight. There was no effect on fetal body weight in the offspring of rats fed diets up to 1% DEHT on GD 0-20 (Faber et al., 2007a). There was an increase in the incidence of rudimentary 14^{th} ribs at the high dose in the study (747 mg/kg-day). However, the toxicological significance of this change is unclear, since a rudimentary 14^{th} rib is a common variation in rats. There was no evidence of developmental toxicity in the offspring of

mice administered DEHT in the diet at concentrations up to 7000 ppm (1382 mg/kg-day) in the diet (Faber et al., 2007a).

DEHT is not genotoxic and it did not cause tumors in a chronic bioassay in rats (Deyo, 2008), although a chronic bioassay in a second species is not available.

5.10 Uncertainties and Data Gaps

Several uncertainties of varying importance were identified in this assessment.

Database:

The overall database on DEHT is fairly complete, including many of the key studies. For most study types there is only one study (i.e., one subchronic study, one chronic study and developmental toxicity study, etc.), with multiple subacute studies but only a single high quality chronic study. It also should be noted that several of the key studies were performed by the manufacturer, Eastman Chemical Company (e.g., Deyo, 2008; Barber and Topping, 1995; Topping et al, 1987). In addition, repeated dose data are available only in rats, with the exception of a single developmental toxicity study in mice (Faber et al., 2007a). Reliable repeat-dose data are available for the oral route only for dietary consumption. Single- and repeat dose dermal studies indicate that DEHT is at worst minimally irritating and non-sensitizing, with no noteworthy systemic health hazards of concern. The limited information available from inhalation studies suggest that DEHT is not a toxicological hazard by the inhalation route, however study details are not available for further review, and the available studies tested relatively low levels.

The key data gap is a repeated dose systemic toxicity study in a second species. Repeated exposure inhalation studies are also lacking, but it is not clear how much exposure would occur via the inhalation route

Hazard:

Body weight: There is some uncertainty in the conclusion that decreased body weight is related to poor palatability of feed dosed with DEHT.

Liver: Effects on the liver were generally limited to increased liver weight across multiple studies, but without histological changes or changes in plasma liver injury biomarkers. Such changes are not considered adverse (U.S. EPA, 2002). The one exception was an increase in the incidence of portal lymphoid foci in males in the chronic study (Deyo, 2008). The etiology of this effect is not known.

Developmental: There is some uncertainty regarding the adversity of the observed variations, and whether the decreased fetal weight is secondary to decreased maternal food

consumption. One study (Faber et al., 2007a) reported increased incidence of rudimentary 14th ribs, however this finding has not been observed in other gestation and reproduction studies.

Ocular: There is uncertainty regarding the causal association between ONL degeneration and DEHT exposure. This lesion is commonly observed with aging in albino rats and may be attributable to photo-toxicity (Deyo, 2008). A better understanding of the causal association between DEHT exposure and ONL is required. Additionally, it is unclear if the mechanism that contributes to this effect in rodents is applicable to humans or sensitive sub populations, such as individuals with albinism.

Respiratory: The significance of the exacerbation of the incidence of the age-related lesion, eosinophilic inclusions of the nasal turbinates in the chronic study (Deyo, 2008), is unclear. It would be of interest to determine whether this endpoint is observed following inhalation exposure.

Table 3. Summary of NOAELs/LOAELs Identified for DHET by Organ System

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
Repeated Dose					
Albino rats (M) 5/dose Eastman Kodak Co. 1975, as cited by Eastman Chemical, 2010; ANSES, 2015	10 days Diet 0, 0.1, or 1.0 % (Equivalent to 0, 85, or 885 mg/kg-day)	NA	NOAEL = 885 LOAEL = NA	NA	No compound-related changes from controls were observed for body weight gain and food, hematology parameters, serum clinical chemistry, liver and kidneys weights, gross pathology and microscopic examination of approx. 20 tissues. GLP compliant
Sprague-Dawley rats (M) 5/dose Eastman Kodak Co., 1983, as cited by Eastman Chemical, 2010; Versar, 2010	14 day Inhalation 8 hours/day, 5 days/week 0 or 46.3 mg/m^3	NA	NOAEL = 46.3 mg/m^3 LOAEL = NA	NA	No significant effects were reported in hematology, serum chemistry, or pathology. The study was poorly described, limiting interpretation. The study was conducted under GLP assurances.

[5] All effect levels as identified by the authors of this assessment.

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
Sprague-Dawley rats (M) 5/dose ANSES, 2015 (no citation to original study)	Inhalation 6 hours/day for 14 days 0 or 71.8 mg/m^3	NA	NOAEL = 71.8 mg/m^3 LOAEL = NA	NA	No significant effects were reported in hematology, serum chemistry, or histopathology.
Sprague Dawley rats (M&F) 5/sex/dose Topping et al., 1987	21 days Diet 0, 0.1, 0.5, 1.0, 1.2, or 2.5% M: 0, 86, 431, 861, 1033, 2154 mg/kg-day F: 0, 98, 490, 980, 1176, 2450 mg/kg-day	Body weight	NOAEL = 1033 (M) NOAEL = 1176 (F) LOAEL = 2154 (M) LOAEL = 2450 (F)	Reduced body weight gain and feed consumption	Decreased feed consumption is possibly due to poor palatability, and thus may not be a toxic response.
		Liver	NOAEL = 1033 (M) NOAEL = 98 (F) LOAEL = 2154 (M) LOAEL = 490 (F)	Statistically significant increase in relative liver weight. No compound-related histological liver changes were observed. Weak peroxisome proliferation observed at the highest dose level.	Relative liver weight is normalized to body weight and changes observed at 2.5% were due almost wholly to reduced body weights, rather than increased absolute liver weight (Topping et al, 1987). DEHT was not observed to have any effect on absolute liver weight. Peroxisome proliferation was likely secondary to decreased food consumption and is not considered relevant to humans

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
Sprague Dawley rats (M&F) 20/sex/dose GLP compliant study Barber and Topping, 1995	90 days Diet 0, 0.1, 0.5 or 1% M: 0, 54, 277 or 561 mg/kg-day F: 0, 61, 309 or 617 mg/kg-day	Liver	NOAEL = 561 (M) NOAEL = 617 (F) LOAEL = NA (M) LOAEL = NA (F)	Significant increase in relative liver weights	Peroxisome proliferation not observed in any treated group. Absolute liver weight also increased, but not statistically significant.
		Hematology	NOAEL = 561 (M) NOAEL (F) = 617 LOAEL = NA (M) LOAEL = NA (F)	Hematology parameters (Hemoglobin, hematocrit, MCV, MCH) statistically altered from controls.	Slight but significant changes in MCH/MCV seen in 0.5% group and higher. The authors concluded that "in the absence of any other indications of anaemia, the changes seen in the 0.5% dose group were not considered to be biologically significant."
Chronic Exposure					
Fischer 344 rat (M&F) 50/sex/dose Deyo, 2008; CPSC, 2014	104 weeks Diet 0, 1500, 6000 or 12000 ppm M: 0, 79, 324 or 666 mg/kg-day	Ophthalmic	NOAEL = 324 (M) NOAEL = 102 (F) LOAEL = 666 (M) LOAEL = 418 (F)	Increased severity of a retinal ONL degeneration (loss of the outer nuclear layer of the retina).	This effect is related to photo-toxicity in albino rats and exacerbation of pre-existing lesions, and so it is likely that the general human population is much less sensitive than rats, although it could be relevant to people with albinism.

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
	F: 0, 102, 418 or 901 mg/kg-day	Body weight	NOAEL = 324 (M) NOAEL = 418 (F) LOAEL = 666 (M) LOAEL = 901 (F)	Terminal body weights significantly lower than controls; body weight gains significantly reduced in high dose animals	Decreased body weight was not due to poor palatability (food consumption was not affected)
		Liver	NOAEL = 324 (M) NOAEL = 901 (F) LOAEL = 666 (M) LOAEL = NA (F)	Increased incidence of portal lymphoid foci (M). Increased relative liver weights (F; no significant changes in males); no reported change in serum enzymes for liver damage.	The relative liver weight of high dose males was elevated relative to control but the difference was not statistically significant.
		Kidney	NOEL = 324 (M) NOEL = 102 (F)	Significantly decreased absolute kidney weights;	Absolute changes in kidney weight were not supported by relative weight changes (bodyweight). Relative weights were significantly decreased from controls among low- and mid-dose males, but *not* high-dose males, and among mid-dose females with increased weight in high-dose females). No significant histologic evidence of kidney lesions reported. Thus the biological significance of the changes in absolute kidney weights is unclear.

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
		Nasal	NOAEL = 666 (M) NOAEL = 418 (F) LOAEL = NA (M) LOAEL = 901 (F)	Eosinophilic inclusions of the nasal turbinates	Considered to be an exacerbation of an age-related finding. There was no indication that this effect is specific to rats, and so it is considered adverse and relevant to humans.
		Tumors	NOAEL = 606 (M) NOAEL (F) = 901 No LOAEL in M or F	N/A	Granular cell lymphomas were increased in the low-dose males, but not at any other dose
Reproductive/Developmental Toxicity					
Sprague-Dawley rat (M&F) 30/sex/dose OECD Test Guideline 416 GLP compliant Faber et al., 2007b; CPSC, 2014	Two-generation: F_0M: 10 weeks prior to and during mating (n=30) F_0F: 70 days prior to mating, during mating, and through	Body weight gain	NOAEL = 316 (0.3%) (F_0M) NOAEL = 273 (0.3 %) (F_0F) NOAEL = 208 (F_1M) NOAEL = 306 (0.3 %) (F_1F) LOAEL = 530 (0.6%) (M) LOAEL = 316 (0.6%) (F)	Significant reductions in body weight gain of high-dose F0 males (weeks 3 and 7) Significant reduction in mean maternal body weights in the 0.6 and 1% DEHT groups in the F1 generation.	Increased spleen and thymus weights were also observed in high-dose F1 and F2 pups. Reductions in body weight were generally accompanied by reductions in feed consumption.

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
	gestation/ lactation (n=30) F1: Similar to F_0 starting on PND 22 Diet 0, 0.3, 0.6 or 1.0% F_0M: 0, 158, 316 or 530 mg/kg-day F_0F: 0, 273, 545 or 868 mg/kg-day F_1M: 0, 208, 422 or 723 mg/kg-day F_1F: 0, 306, 630 or 1034 mg/kg-day	Reproductive	NOAEL = 530 (1.0 %) (F_0M) NOAEL = 868 (1.0 %) (F_0F) NOAEL = 723 (1.0 %) (F_1M) NOAEL = 1036 (1.0 %) (F_1F) LOAEL = NA	No reproductive effects were reported at any dose level for any generation. Sperm evaluations were performed on F0 and F1 males from all groups. Reproductive parameters (fertility, mating, days between pairing and coitus, gestation, parturition, and estrous cycling)	F1 and F2 mean live liter sizes, numbers of pups born, percentages of males per litter at birth and postnatal survival were unaffected by parental treatment at all concentrations.
		Developmental	NOAEL = 158 (0.3 %) (F_1M) NOAEL = 868 (1.0 %) (F_1F) LOAEL = 315 (0.6 %) (F_1M) LOAEL = NA (F_1F)	F1 males reported to have reduced birth weights; decreased growth; decreased mean body weight	Effect level based on maternal dose. No other signs of developmental toxicity
		Mortality	NOAEL = 530 (1.0 %) (F_0M) NOAEL = 545 (0.6 %) (F_0F) NOAEL = 723 (1.0 %) (F_1M) NOAEL = 630 (0.6 %) (F_1F)	Mortality in F0 and Fi dams.	Single male deaths occurred in the F0 control and mid-dose groups and in the F1 high-dose group but were not considered by the study authors to be related to treatment

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
			LOAEL = NA (M) LOAEL = 868 (1.0%) (F_0) LOAEL = 1034 (1.0 %) (F_1)		
		Liver	NOAEL = 868 (1.0 %) (F_0F) NOAEL = 1034 (1.0 %) (F_1F)	Significant increases in absolute (F0) and mean relative liver weights (both generations) among females at the mid and high doses, but were not considered adverse	No morphological evidence of liver damage, and so the changes were considered to be adaptive.
Sprague-Dawley rat 10/dose (F) Faber et al., 2007a	PNDs 19-21 Gavage in corn oil 0, 20, 200 or 2000 mg/kg-day	Endocrine disruption	NOAEL = 2000 LOAEL = NA	Estrogenic activity	No effects on estrogenic activity. GLP compliant developmental toxicity study (OECD 414).
		Development	NOAEL = 200 LOAEL = 2000	Reduced body weight gain of immature treated females.	Reduced mean body weight gain in the high-dose group resulting in a 19% reduction in mean body weight gain over the entire treatment period.

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
Sprague-Dawley rat 8/dose (F) Not GLP Gray et al., 2000	Gestation day 14 to PND 3 Gavage 0 or 750 mg/kg-day	Endocrine disruption in male pups	NOAEL: 750 LOAEL: NA	No signs of demasculinization or male reproductive tract malformations in male pups.	No anti-androgenic effects were observed. A slight decrease in serum testosterone was reported, but did not reach statistical significance. Maternal effects and litter weight and pup number recorded, but focus was on male pups.
Sprague-Dawley rat (F) 25/dose Faber et al., 2007a	Gestation days 0-20 Diet Administered concentrations: 0, 0.3, 0.7, and 1.0% (w/w) 0, 226, 458 or 747 mg/kg-day	Body weight (Maternal)	NOAEL = 458 LOAEL = 747	Reductions in mean and net body weight gains.	Minor changes in organ weights not considered adverse. Increased liver weight of 10% not considered adverse in the absence of histopathology.
		Liver	NOAEL = 747 LOAEL = NA	A significant increase in absolute liver weight reported for high-dose rats.	
		Developmental	NOAEL = 458 LOAEL = 747	Increased incidence of rudimentary 14th ribs.	GLP compliant developmental toxicity study (OECD 414). Rudimentary 14th rib is a common variation and the biological significance of the increase is unclear.
ICR Mouse 25/dose (F)	Gestation days 0-18 Diet	Developmental	NOAEL = 1382 LOAEL = NA	NA	Minor changes in organ weight not considered adverse; no anti-androgenic effects were observed

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[5]	Toxicological Basis	Comments
Faber et al., 2007a; CPSC, 2014	Administered concentrations: 0, 1000, 3000, or 7000 ppm 0, 197, 592 or 1382 mg/kg-day	Liver	NOAEL = 1382 LOAEL = NA	Changes in maternal liver weights were seen in the mid- and high-exposure level animals.	Increased liver weights were considered adaptive.

6 Exposure

The use of DEHT in consumer products has been described in Section 3 of this report .

No information could be found on leaching or migration of DEHT from polymer resins. Information on total exposure is also not available (CPSC, 2014). However, CPSC (2014) estimated infant exposure to plasticizers from mouthing soft plastic objects except pacifiers. Based on the mean migration rate and mouthing duration, mean exposure was estimated at 0.69, 0.45, and 0.41 μg/kg-day for babies aged 3 - <12 months, 12 months - <24 months, and 24 - <36 months, respectively. The upper bound exposure was 2.8 μg/kg-day. CPSC (2014) further noted that DEHT was present in about one-third of the toys and child care articles tested by CPSC (Dreyfus, 2010).

DEHT is approved by the FDA and European regulatory agencies for use in food contact applications, including use in closures with sealing gaskets and in vinyl chloride polymer fomulations (Ball et al, 2012; Silva et al., 2017).

In adults, exposure is expected to be limited primarily to the dermal route. The systemic dose from dermal exposure is limited by the very low dermal absorption (0.103 ± 0.052 μg/cm^2/hr), and the limited number of objects resulting in direct ongoing dermal contact. ANSES (2015) stated that consumer products creating a potential for exposure are limited to "coated fabrics," which are waterproofed using a flexible vinyl coating. Exposure is further limited by the coating being only on the "outside" of the fabric (i.e., the side that is not in direct contact with the skin). DEHT was reported as the most common plasticizer in children's backpacks and plastic toys (Xie et al., 2016, as reported by Sheikh et al., 2016). The potential for human exposure was noted, based on correlations between the mass of DEHT in these object and the amount of DEHT on dry and wet wipes of these materials.

No information was located on concentrations of DEHT in environmental media. However, exposure via environmental media is likely to be limited; the single global manufacturer uses a closed system for production, and thus there is limited potential for substantial environmental release during manufacture (OECD, 2003). Based on its physical properties (very low water solubility and very low vapor pressure, it is likely that DEHT released to the environment will adhere strongly to soil or sediment, and will not easily enter or persist in the air or in water (OECD, 2003). It is reasonable to expect that releases to the environment from disposal of consumer products is a possibility.

<u>Biomonitoring</u>

Two studies were located that used biomonitoring for DEHT-specific metabolites to evaluate DEHT exposure. Lessman et al. (2017) estimated the daily total intake of DEHT in 107 Portuguese children (4–17 years old) based on levels of the DEHTP-specific metabolite mono(2-

ethyl-5- carboxypentyl) terephthalate (5cx-MEPTP) in urine. They found that this metabolite was detectable in all of the samples evaluated. Consistent with the use of DEHT in food-contact applications, they found that the calculated daily DEHTP intakes were higher in children who consumed their normal diet, than in children who received guidance to eat fresh and unprocessed foods. The median daily DEHTP intake of the overall study population was calculated to be 0.67 µg/kg-day (95th percentile 6.25 µg/kg-day. Significantly higher (p=0.045) intakes were estimated for children aged 4-11 years (n=68, mean of 0.71 mg/kg-day) than for children aged 12-17 years (n=39, mean of 0.36 mg/kg-day).

In the second biomonitoring study, Silva et al. (2017) investigated the exposure to DEHT in a convenience sample of male and female adults in the U.S. Spot samples of urine collected in 2000 (*N* = 44), 2009 (*N* = 61), 2011 (*N* = 81), 2013 (*N* = 92), and 2016 (*N* = 149) were analyzed for two major DEHTP oxidative metabolites: mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP) and mono-2-ethyl-5-hydroxyhexyl terephthalate (MEHHTP). Both metabolites were detected in all samples collected in 2016, and the concentrations increased from 2000 to 2016, consistent with the increasing use of DEHT in place of DEHP.

7 Discussion

7.1 Toxicity Under FHSA

No data were available on the effects of DEHT in humans, except for one study that demonstrated that DEHT is not irritating and non-sensitizing to human skin (David et al., 2003).

It is not clear whether **DEHT fits the designation of "acutely toxic" under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A))** following single oral exposures. Acute LD_{50} values for DEHT in rats were described as >3200 mg/kg, but it is not clear how high the LD_{50} is (as cited in Versar, 2010; Eastman Chemical, 2010; Ball et al., 2012). In addition, SCENIHR (2008) reported an LD_{50} of 5000 mg/kg, although it is not clear if the authors intended this to be >5000 mg/kg. It appears that **DEHT 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 dermal exposures. The 24-hour dermal LD_{50} in guinea pigs was >20 mL/kg (>19,680 mg/kg) (Eastman Kodak Co., 1975, as reported by Versar, 2010; Ball et al., 2012). No dermal LD_{50} in rabbits is available. The available acute inhalation studies reported no toxicity, but were not conducted at high enough concentrations to determine whether DEHT is acutely toxic under the FHSA. Dermal exposure to DEHT caused minimal irritation in volunteers (David et al., 2003; Lockhart 2001a, as reported by Versar, 2010; ANSES, 2015; OECD, 2003), and was non-irritating to rabbits (Product Safety, 2006a; as cited by Ball et al., 2012; ANSES, 2015), although it was moderately irritating to guinea pigs administered a single high dose (Eastman Kodak Co., 1975, as reported by Versar, 2010; Ball et al., 2012) or repeated doses (no citation provided for the primary study, as cited by ANSES, 2015; ECHA, 2012). DEHT caused only slight irritation in eye irritation studies (Eastman Kodak Co., 1975, as cited by Versar, 2010; ECHA, 2012, as cited by ANSES, 2015; ToxServices, 2012; Teehaar, 1975, as

cited by ANSES, 2015). DEHT was not considered to be an eye irritant (ECHA, 2012, as cited by ANSES, 2015; ToxServices, 2012). Dermal exposure to DEHT was not a sensitizer in humans (David et al., 2003; Lockhart, 2001b) or guinea pigs (ToxServices, 2012; ANSES, 2015).

DEHT did not elicit signs of sub-acute oral (Eastman Kodak Co. 1975, as cited by Eastman Chemical, 2010; ANSES, 2015) or inhalation toxicity in rats following 10-day exposures (Eastman Kodak Co., 1983c, as cited by Eastman Chemical, 2010; Versar, 2010).

Sufficient animal data exist to support the conclusion that DEHT can be considered "toxic" under the FHSA, although there are caveats to much of the observed toxicity. Decreased body weight was observed at durations ranging from 21 days to 2 years (Topping et al., 1987; Deyo, 2008; Faber et al., 2007b). Although in many cases it appeared to be secondary to decreased food consumption as a result of poor palatability, it was observed in the chronic study (Deyo, 2008) in the absence of decreased food consumption. Increased liver weight was considered adaptive when in the absence of other changes, but it also occurred in the presence of weak peroxisome proliferation (Topping et al., 1987) and increased periportal lymphoid foci (Deyo, 2008). Exacerbation of retinal ONL degeneration and of eosinophilic inclusions of the nasal turbinates were also observed following chronic exposure (Deyo, 2008), although rats are likely to be much more sensitive than humans (except those with albinism) to the former effect.

DEHT is not a reproductive toxin. No reproductive effects were seen in the two generation rat feeding study (Faber et al., 2007b), no uterotropic (estrogenic) effects in the offspring of rats treated on PND 19-21 (Faber et al., 2007a) and no evidence of demasculinization (an antiandrogenic effect) in the male offspring of rats gavaged on GD 14 – PND 3 (Gray et al., 2000). There was also no effect on male or female reproductive organs in the subchronic (Barber and Topping, 1995) or chronic (Deyo, 2008) studies. .

The developmental toxicity of DEHT is low. Decreased pup weight was seen in the 2-generaiton study (Faber et al., 2007b), although these changes may have been secondary to decreased maternal weight. There was no effect on fetal body weight in rats or mice in developmental toxicity studies (Faber et al., 2007a). There was no evidence that DEHT caused increased incidence of external malformations of variations in rats or mice (Faber et al., 2007a,b). The incidence of rudimentary 14^{th} ribs was slightly elevated in fetuses from rats receiving DEHT at 747 mg/kg-day.

DEHT is not genotoxic and it did not cause tumors in a chronic bioassay in rats (Deyo, 2008), although a chronic bioassay in a second species is not available.

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APPENDIX 1

Search Terms Used

“Bis(2-ethylhexyl) terephthalate” OR “Di-(2-ethylhexyl) terephthalate” OR “1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester” OR "1,4-Benzenedicarboxylic acid, 1,4-bis(2-ethylhexyl) ester" OR “ADK Cizer D 810” OR “DEHTP” OR “Dioctyl terephthalate” OR “DOTP” OR “Terephthalic acid, bis(2-ethylhexyl) ester” OR “Eastman 168” OR “Kodaflex DOTP” OR “NEO-T” OR “Palatinol DOTP” OR “UN 488” OR “Plasticizer 168” OR (6422-86-2)

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).