CPSC Staff Statement on University of Cincinnati Report
"Toxicity Review for Dibutyl Sebacate (DBS)"[1]

June 2019

The U.S. Consumer Product Safety Commission (CPSC) contracted with the University of Cincinnati to conduct toxicology assessments for nine dialkyl o-phthalate (o-DAP) substitutes: phenyl esters of C10-C18 alkylsulfonic acid esters (ASE); glycerides, castor-oil-mono-, hydrogenated, acetates (COMGHA); dibutyl adipate (DBA) and di-isobutyl adipate (DiBA); di (2-ethylhexyl) sebacate (DEHS)/dioctyl sebacate (DOS); a mixture of 98% di-2-ethylhexyl terephthalate (DEHT) and 2% 2-ethylhexyl methyl terephthalate (2-EHMT); dibutyl sebacate (DBS); diisononyl adipate (DINA); epoxidized soybean oil (ESBO); and tributyl citrate (TBC). The reports will be used to inform staff's assessment of products that may contain these compounds and is the first step in the risk assessment process.

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

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

The toxicity review for DBS follows. Based on the research conducted by the University of Cincinnati, the animal data were sufficient to support the conclusion that DBS does not fit the designation of acutely toxic under the FHSA following single oral exposures. DBS has not been tested to high enough concentrations in air to determine whether it is toxic via the inhalation route.

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

TOXICITY REVIEW FOR
DIBUTYL SEBACATE
(DBS)

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1 Introduction

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with dibutyl sebacate.

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

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

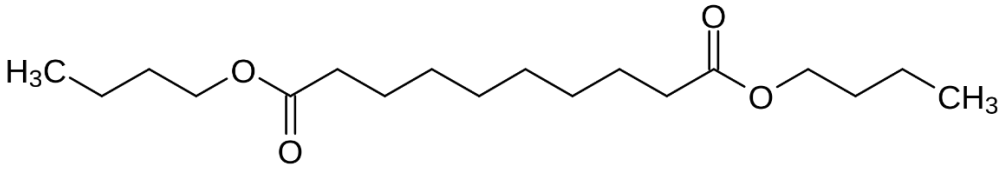
Searches were conducted for studies indexed to PubMed and Toxline databases from all dates to the date of the search (July, 2018). Other databases and websites were also used to identify additional key information, particularly authoritative reviews. Authoritative reviews for general toxicity and physicochemical information were identified in the following databases using the CAS number for DEHS/DOS and synonyms. Downloaded documents were saved as pdfs. The sites searched included:

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

- FDA (https://www.fda.gov/)
- Health Canada (https://www.canada.ca/en/health-canada.html)
- IARC (https://www.iarc.fr/)
- INCHEM (http://www.inchem.org/)
- JEFCA (http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/)
- NICNAS (https://www.nicnas.gov.au/)
- NTP (https://ntp.niehs.nih.gov/)
- OECD (http://www.oecd.org/)
- WHO (http://www.who.int/en/)

2 Physico-Chemical Characteristics

Table 1: Physical-Chemical Characteristics

Chemical Name	Dibutyl Sebacate
Synonyms	Bis(n-butyl) sebacate; Bis(n-butyl)sebacate; Butyl sebacate; Di-n-butyl sebacate; Di-n-butylsebacate; Dibutyl 1,8-octanedicarboxylate; Dibutyl decanedioate; Dibutyl sebacinate; Decanedioic acid, dibutyl ester (ChemIDplus, 2018)
CAS Number	109-43-3
Structure	
Chemical Formula	$C_{18}H_{34}0_4$
Molecular Weight	314.463 g/Mol
Physical State	Oily liquid
Color	Colorless
Melting Point	-10ºC

Boiling Point	344.5ºC
Vapor Pressure	4.69 x 10^{-6} mm Hg at 25℃
Water Solubility	40 mg/L at 20ºC
Log Kow	6.01 (predicted average) (U.S. EPA, 2018a)
Log Koc[1]	6.07 x 10^{3} L/kg (predicted average) (U.S. EPA, 2018a)
Henry's Law	2.39 x 10^{-7} atm-m^3/mole (predicted average) (U.S. EPA, 2018a)
Flashpoint	353ºF
Density	0.941 g/cm^3 (predicted average) (U.S. EPA, 2018a)
BCF	77 (PubChem, 2018) 95.8 (predicted average) (U.S. EPA, 2018a)
Source	HSDB (2018), unless otherwise stated

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

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

3 Manufacture, Supply, and Use

Manufacture and Supply

DBS is a high production volume chemical both in the U.S. (U.S. EPA, 2018b) and in Europe (OECD, 2018). U.S. manufacture and imports were reported to be between 500,000 and 1,000,000 pounds (250 to 500 tons) per year for 2015 (U.S. EPA, 2018). DBS is manufactured and/or imported into the European Economic Area at a rate of 100 - 1000 tons per year (ECHA, 2018a).

Use

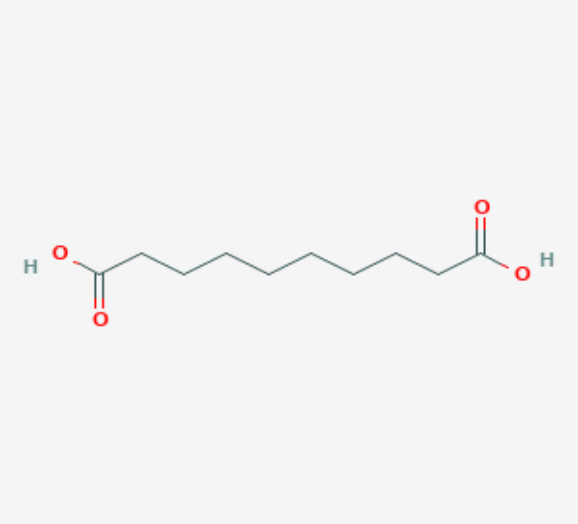
DBS is a popular plasticizer used in a variety of diverse applications as a component of both solid and liquid products. DBS is part of the U.S. EPA's Safer Choice program's "safer chemical" list for the functional use classes of emollients, skin conditioning agents, and solvents (U.S. EPA, 2018c). DBS is also used in toys, inks, toners, colorant products, photographic supplies, films, perfume and cosmetics, paints, motor oil, washing and cleaning products, plant protection products, lubricants and greases, adhesives and sealants, polishes and waxes, and coatings for medications (Abe et al., 2012; ECHA, 2018a; PubChem, 2018, Hauser et al., 2004).

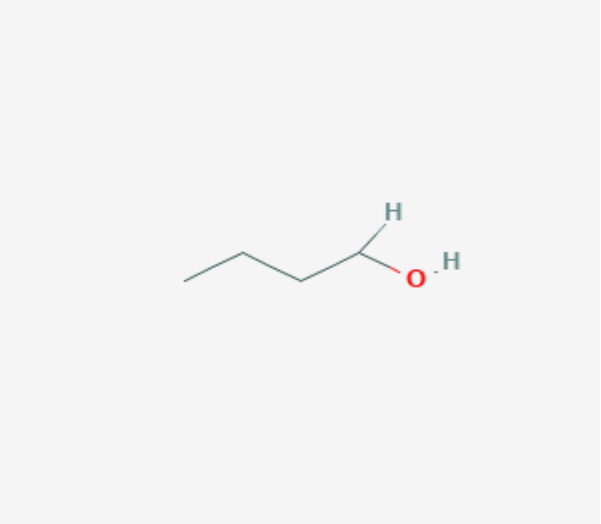
DBS may be used as a food additive for direct addition to food as a synthetic flavoring substance and adjuvant (HSDB, 2018; JECFA, 2002). It is also an indirect food additive, resulting from its use in food-contact applications such as wrapping film, food packaging, and as a component of adhesives (HSDB, 2018; Bui et al., 2016). It is reported to be used as a flavor ingredient in non-

alcoholic beverages, ice cream, candy, and baked goods (HSDB, 2018) and in gaskets of glass jar food lids (Rothenbacher and Schwack, 2010). It is also used as an excipient in drug formulations (FDA, 2014).

4 Toxicokinetics

No standard toxicokinetic studies have been conducted with DBS, and very little information is available on the toxicokinetics of DBS. In particular, it is unclear whether the low toxicity of DBS, particularly via the oral route, is related to low absorption or efficient metabolism. However, some specialized studies of metabolism have been conducted. Smith (1953) reported that pancreatic lipase hydrolyzed DBS *in vitro*, and hydrolysis of DBS to sebacic acid and butanol (presumably n-butanol) has been reported in intestinal fluid (SCF, 1997, as cited by BIBRA, 1998). The structures of sebacic acid and n-butanol are shown below.





Sebacic acid

n-butanol

5 Hazard Information

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

The acute oral toxicity of DBS is very low; ATSDR (1995) concluded that DBS is relatively non-toxic.

ECHA (2018b, citing Anonymous, 1976) reported an LD_{50} in a "key study" of >5 mL/kg (>4700 mg/kg, based on density of 0.94 g/mL). A single gavage dose (5 mL/kg) was administered undiluted to 5 male and 5 female Albino rats. ECHA (2018b) noted that the experimental details were lacking; it appears that this study was not summarized in other secondary sources.

Higher LD_{50}s were determined in a number of other studies, ranging from 14,870 to 32,000 mg/kg, but secondary sources noted methodological deficiencies or incomplete information for these studies.

In an early study, Smith (1953) evaluated administered DBS by gavage to male Sprague Dawley rats at doses up to 32,000 mg/kg and monitored them for 7 days. At 16,000 mg/kg, 6/6 rats survived, while 6/6 died at 32,000 mg/kg. Smith (1953) did not report an LD_{50}, but ECHA (2018b) reported an LD_{50} of 24,000 mg/kg from this study. Clinical signs of toxicity were not reported, but minimal decreased body weight gain was reported at 8000 and 16,000 mg/kg.

Lawrence et al. (1994) reported an LD_{50} of >32 mL/kg (30,080 mg/kg, based on a density of 0.94 g/mL) in mice. Dose levels (up to 16 mL/kg) were specified only for the pretest conducted with 2 mice/sex/dose; no information was provided on the number of mice tested in the definitive test, or on clinical signs in the pretest or definitive test.

Information on clinical signs of toxicity was available only from studies published in other languages and reported only in secondary sources. Astapova et al. (1990) and Komerova (1976, both as cited by BIBRA, 1998; ECHA, 2018b) reported LD_{50}s of 19,500 and 26,250 mg/kg in mice and rats, respectively, with the deaths attributed to hemolytic instability and lung function failure. However, ATSDR (1995) noted that the observed effects may have been a result of aspiration of the gastric contents due to the high gavage volumes used. Effects on the heart muscle, kidneys, brain, stomach and intestinal walls were also reported (Komerova, 1976, as cited by BIBRA, 1998). In another rat study, gastrointestinal hypermotility and diarrhea, impaired liver function, and general depression were reported in rats, with an LD_{50} of 14,870 mg/kg (Kushneva et al., 1999, as cited by RTECS). The confidence in these reported effects is low, due to the incomplete reporting.

5.1.2 Acute Dermal Toxicity

Application of an unspecified volume of 100% DBS to rabbit skin for 48 hours did not result in any animal deaths (Mallette and Von Haam, 1952). No further details were provided regarding doses, sex, or numbers of animals.

ECHA (2018b, citing Smyth et al., 1951) reported a dermal LD_{50} of 20 mL/kg in rabbits for dibutyl adipate, under conditions of occluded testing, and applied this value to DBS using a read-across category approach. Although only limited study information is available and the data are extrapolated from another related chemical, the results are consistent with low dermal toxicity of DBS.

5.1.3 Acute Inhalation Toxicity

Two studies are available for acute inhalation exposure to DBS, but neither were conducted according to modern testing methods, and so the conclusions from both studies are severely limited. Union Carbide (1983, as cited by BIBRA, 1998) reported on a study in which DBS mist was created by bubbling a stream of air through DBS plasticizers held at 170°C. After 30 minutes of exposure there were no fatalities, but 1-hour of exposure resulted in the death of all

six exposed rats. The exposure concentration was not measured, but was judged by the study authors to be approximately (within an order of magnitude) at saturation, although the exposure may have included oxidation products.

Astapova et al. (1990, as cited by ECHA, 2018b; BIBRA 1998; and RTECS, 2018) exposed rats to 5.4 mg/m^3 DBS (reported as a saturated concentration created at 50°C) (0.005 mg/L air) for 4 hours, and mice to the same concentration for 2 hours. Reported effects were impaired metabolism in tissue, failure in liver function, reduced reactivity, and dystrophic processes in unspecified organs, but no mortality. ECHA reported that an insufficiently high concentration was tested. Note that the testing of the surrogate (described in the next paragraph) used aerosol exposure, rather than vapor exposure, perhaps due to limitations on the concentration of DBS vapor that can be attained.

ECHA (2018b), citing two unpublished reports (Anonymous, 1989a, Anonymous 1998), listed LC_{50}s for two unnamed trade substances in a read-across for DBS. An LC_{50} of >5.7 mg/L (>5700 mg/m^3) was reported from testing of an unspecified trade material in SPF Wistar/Chbb:THOM male and female rats exposed to an aerosol (head only) for 4 hours. In the second study, an LC_{50} of >3.2 mg/L (>3200 mg/m^3) was reported from testing of an unspecified trade material in Sprague-Dawley male and female rats (5 each) exposed to an aerosol by whole body for 4 hours. The validity of this read-across analysis cannot be verified in the absence of chemical identity information.

5.1.4 Irritation/Sensitization

Dermal Irritation

Several studies looked at the effects of DBS applied to the skin of volunteers. DBS was not irritating when an unspecified volume of neat solution was applied to the skin of 15-30 volunteers for 48 hours (described by BIBRA, 1998 as a covered patch test) (Mallette and Von Haam, 1952). There was also no irritation when a 10% solution in petrolatum was applied to the skin of 20 volunteers for 48 hours (de Groot et al., 1991, and as cited by BIBRA, 1998). No irritation was observed when DBS was applied to abraded (*sic*) skin of an unspecified number of volunteers (no dosage or duration reported) (Askarova and Muryseva 1975, as cited by ATSDR, 1995).

In an animal test of dermal irritation, undiluted DBS was applied to the shaved and abraded skin of three male and three female rabbits in a study generally conducted according to guidelines, except that exposure was for 24 hours, the site was occluded, and the rabbits were examined at 24 and 72 hours after patch removal (Anonymous, 1976, as cited by ECHA, 2018b). The only evidence of irritation was erythema (grade 1 of 4) in one rabbit at 24 hours. The authors concluded that DBS was not irritating. Mallette and Von Haam (1952) observed no skin irritation in a group of two to four rabbits dermally treated with an unspecified volume of neat DBS) for 48 hours. Komarova (1976, 1979, as cited by ATSDR, 1995) observed slight dermal

irritation to rabbits and guinea pigs following application of DBS, but no experimental details were provided.

Sensitization

A pharmacy assistant who had been sensitized to a lotion containing di-isopropyl sebacate reacted to both di-isopropyl sebacate and to DBS (1-10% in petrolatum) in follow-up patch testing (De Grott et al., 1991). In contrast, 20 unexposed controls did not react to the highest concentration of DBS. Among 15-30 volunteers treated with an unspecified dose of neat DBS for 48 hours, no sensitization was observed when the subjects were re-exposed 2 weeks later (Mallette and von Haam, 1952). Workers exposed to lubricants containing DBS reportedly had a sensitization rate of 3.3% (Askarova and Muryseva, 1975, as cited by ATSDR, 1995). The route (inhalation or dermal) and exposure concentration/dose were not available. Patch testing was conducted using concentrations of DBS previously shown to be non-irritating. Further details were not available.

In rabbits treated with a non-irritating dermal dose of DBS for 48 hours, and then challenged 2 weeks later (apparently at the same dose), no skin sensitization was observed (Mallette and Von Haam, 1952). In addition, the rabbit is not the preferred species for sensitization testing under modern test methods.

Anonymous (1989b, as cited by ECHA, 2018b) conducted an OECD Guideline 406 guinea pig maximization test with the structurally related compound dibutyl adipate (DBA), which ECHA (2018b) applied to DBS in a read-across analysis. In the induction period, 20 female Albino guinea pigs were exposed to either (1) intradermal injection of DBA (50% in Freund's complete adjuvant (FCA), 20% by volume in corn oil, or 20% by volume in Freund's complete adjuvant/water), or (2) 48 hours (epicutaneous with occlusion) exposure to neat DBA, preceded by pretreatment with 10% SDS 24 hours prior to exposure. Both the injection and epicutaneous exposures were conducted twice, separated by 7 days. Groups of 10 control animals were treated with corn oil and/or FCA alone. In the challenge exposure, the guinea pigs were exposed cutaneously 21 days later for 24 hours, and evaluated at 48 and 72 hours. Signs of irritation, including erythema and edema, were observed in the induction phase, but there was no evidence of sensitization in the challenge phase.

Eye Irritation

In a guideline-compliant eye irritation study conducted according to Good Laboratory Practices (GLP), three male Kleinrussen Chbb-HM rabbits were treated with 0.1 mL[1] neat DBS for 24 hours, and observed at 1, 24, 48 and 72 hours (Anonymous, 1991, as cited by ECHA, 2018b). Two rabbits had an average conjunctivae score across three time points of 0.33 (indicating one time point with a score of 1 on a scale of 3), and one rabbit had an average chemosis score of

[1] The volume was not reported by ECHA (2018b), but is specified in the test guideline.

0.33 (on a scale of 4). The authors concluded that DBS was not irritating to the eye. In another study with six Albino rabbits treated with neat DBS in the eye and observed for up to 7 days (Anonymous, 1976, as cited by ECHA, 2018b), redness of the conjunctivae was seen in four rabbits at 24 hours and one rabbit at 48 hours. The score was 1 on a scale of 4, except for one rabbit at 24 hours. The authors concluded that DBS was not irritating to the eyes. No eye irritation was reported when DBS was applied to the conjunctival sacs of guinea pigs (Komarova, 1976, as cited by BIBRA, 1998), but details were lacking.

5.2 Repeated Dose Toxicity

Oral

FDA (2014) summarized several studies of DBS conducted by Pfizer in support of the use of DBS as an excipient and intended to fulfill the requirements of ICH M3(R2) (ICH, 2009). All of the studies were unpublished reports for which the final report date was unavailable, so they are cited based on the reported date of study initiation. In a 26-week study compliant with Good Laboratory Practices (GLP) (Pfizer, 2014a, as cited by FDA, 2014), male and female Crl:WI(Han) rats (15/sex/dose) were treated with DBS by daily gavage (in a proprietary water-based vehicle) at doses of 0, 100, 300, or 1000 mg/kg-day. Clinical signs during treatment included discolored haircoat around the perineal area in females and thinning haircoat in males, but the observations were not dose-related and were not associated with any other changes and so were not considered adverse. There was no effect on body weight, food consumption, ophthalmoscopy, hematology, urinalysis, clinical chemistry, organ weight or histopathology at any dose. The high dose of 1000 mg/kg-day was the study NOAEL

In a similar GLP-compliant study in dogs (Pfizer, 2014b as cited by FDA 2014), beagle dogs (4/sex/dose, age 13-14 months) were administered DBS at 0, 100, 300, or 1000 mg/kg-day by oral gavage in a proprietary water-based vehicle. A transient incidence of swollen vulva was seen in all treated groups but was not correlated with other findings. This effect was considered treatment-related but not adverse. Excessive salivation was seen in females but not in males, and was not considered adverse. There was no effect on body weight, food consumption, ophthalmoscopy, electrocardiogram (ECG), hematology, urinalysis, clinical chemistry, organ weight or histopathology at any dose. The high dose of 1000 mg/kg-day was the study NOAEL

In a poorly reported study, with limited details in the secondary source, Komarova (1976, as cited by BIBRA, 1998) treated rats and mice (number/group not available) with doses up to 1/50 of the LD_{50} (interpreted by BIBRA, 1998 to be oral daily doses of 350 mg/kg-day) for 9 months. There was no effect on growth or behavior, or on blood composition or liver enzyme function. There were also no “tissue abnormalities” (extent of evaluation not reported). There were also no signs of toxicity in rats and mice administered up to about 3500 mg/kg-day for 1.5 months. This study is not presented in Table 2 due to insufficient study details and concerns about study quality.

Inhalation

Astapova et al. (1990, as cited by BIBRA, 1998) exposed rats and mice (number/group not reported) to DBS vapor at concentrations of 0.07, 0.63, or 6.2 mg/m^3 for 4 months. A Lim(ch) (interpreted by BIBRA as a threshold of a "chronic" effect) was reported as 0.63 mg/m^3, but no further details were provided, including information on the number of hours/day or whether exposure was continuous.

5.3 Chronic Toxicity/Carcinogenicity

Smith (1953) treated 5-week-old male Sprague Dawley rats (10/dose) with DBS in the diet at 0, 0.01, 0.05, 0.25, or 1.25% of the diet for 1 year. Using a food factor of 0.069 for a chronic study with male Sprague-Dawley rats (U.S. EPA, 1988), the corresponding doses are 0, 6.9, 34.5, 172.5 and 862.5 mg/kg-day[2]. Body weight and food intake were measured, but the doses in mg/kg-day were not reported. Hematology (hemoglobin, total erythrocytes, and total and differential leucocyte counts) was evaluated at 3, 6, and 9 months. Histopathology of the lungs, heart, liver, spleen, adrenals, kidneys, stomach, small intestine, thyroid and brain was also evaluated.

In a related 2-year study, Smith (1953) administered DBS at 0, 0.01, 0.05, 0.25, 1.25, or 6.25% of the diet to 5-6 week old male Sprague-Dawley rats (16/dose, and 32/control). Using a food factor of 0.069 for a chronic study with male Sprague-Dawley rats (U.S. EPA, 1988), the corresponding doses are 0, 6.9, 34.5, 172.5, 862.5, and 4312 mg/kg-day[3]. Body weight and food intake were monitored. Hematology was evaluated at 6, 12, 18, and 24 months. Necropsies were conducted on 3 rats/dose at the end of 1 year, and histopathology was evaluated as in the 1-year study.

No treatment-related changes were observed in either the 1-year or the 2-year studies. The incidence of pneumonitis was elevated in the high-dose group in the 2-year study (no statistics were reported), but the increase was not dose-related and the incidence in the high DBS dose was comparable to the incidence in the controls in a separate study with butyl stearate. Thus, the high dose was a NOAEL in both studies. This was 1.25% in diet, or 862.5 mg/kg-day in the 1-year study, and 6.25% in diet, or 4312 mg/kg-day in the 2-year study. Although these chronic studies were reasonably well conducted for their time, they were conducted prior to the development of modern test methods, tested fewer animals than guideline for chronic studies, and the list of tissues evaluated was much less extensive than modern methods.

5.4 Reproductive Toxicity

FDA (2014) reported on a 1-generation reproductive toxicity study in rats (Pfizer, 2014c). In this GLP-compliant study, Crl:CD(SD) rats (20/sex/group) were treated by oral gavage in a proprietary water-based

[2] BIBRA (1998) apparently used a default food factor of 0.05, and determined that the high dose corresponded to 3100 mg/kg-day.
[3] BIBRA (1998) apparently used a default food factor of 0.05, and determined that the high dose corresponded to 3100 mg/kg-day.

vehicle with 0, 100, 300, or 1000 mg/kg-day. The doses were chosen based on the results of Smith (1953) and based on the high dose of 1000 mg/kg-day being identified by ICH as an appropriate limit dose. Males were treated for "at least 28 days" prior to mating, during the mating period, through sacrifice after "at least 10 weeks of treatment." Females were dosed for at least 14 days prior to mating, during the mating period and through gestation day (GD) 7, and were sacrificed on GD 14. DBS treatment had no effect on clinical signs; body weight during the premating, mating or pregnancy phases; food consumption, or fertility parameters (e.g., mating/fertility index, corpora lutea, preimplantation loss) at any dose. Necropsy results were all normal. The FDA identified the high dose of 1000 mg/kg-day as the study NOAEL. However, even though FDA considered the study acceptable, there were several limitations. No mention was made of whether a number of important parameters were evaluated, including histopathology of reproductive organs or analysis of sperm parameters, estrus cycle, or endocrine-related endpoints. In addition, the exposure of the males prior to mating was insufficient for evaluation of effects on the entire spermatogenic cycle.

Smith (1953) treated 5-6 week old Sprague Dawley rats (20/sex) with 6.25% DBS in the diet for 10 weeks prior to mating; the control group had 10 rats/sex and was treated for the same period. The diet can be estimated to have delivered a dose of 4312 mg/kg-day using a strain-specific food factor of 0.069 (U.S. EPA, 1988); BIBRA (1998) calculated a dose of 3100 mg/kg-day, apparently using a generic food factor of 0.05. Litters were weaned on postnatal day (PND) 21, and randomly selected pups (24/sex/dose) were fed the same diet as had been ingested by their parents for an additional 21 days, prior to sacrifice. Based on a food factor of 0.147 for weanling Sprague-Dawley rats, the dose to the pups is estimated at 9188 mg/kg-day. There was no effect on fertility or on pup survival, but there was a significant ($p<0.01$) decrease in the pup weight at weaning and weight gain at PND 42. This decrease was seen in both males and females and was >10% at weaning and was >20% at PND 42, but the dose-response could not be evaluated, since only one dose level was tested. The authors reported no gross pathology in the offspring sacrificed on PND 42, but it appears that histopathology was not evaluated. The study is also limited by minimal reporting of the endpoints evaluated and because of the small size of the control group. The single dose tested of 6.25% in feed, or 4312 mg/kg-day (dams) was a developmental LOAEL, but a systemic and reproductive NOAEL.

5.5 Prenatal, Perinatal, and Post-natal Toxicity

FDA (2014) reported on a GLP-compliant developmental toxicity conducted in Sprague Dawley rats (22 pregnant females/dose) gavaged daily with 0, 100, 300, or 1000 mg/kg-day DBS in a proprietary water-based vehicle on GD 6-17 and sacrificed on GD 21 (Pfizer, 2014d). The selected doses were based on the results of Smith (1953) and based on the high dose of 1000 mg/kg-day being identified by ICH as an appropriate limit dose. There were no treatment-related clinical signs of toxicity, and no effects on body weight, food consumption, cesarean section data (e.g., implantation sites, pre- and post-implantation loss), or on the offspring (e.g., malformations, variations). The study summary did not report whether fetal weights were recorded. The high dose of 1000 mg/kg-day was the study NOAEL for both maternal and developmental effects.

FDA (2014) reported on a GLP-compliant developmental toxicity conducted in Hra: (NZW)SPF rabbits (22 pregnant females/dose) gavaged daily with 0, 100, 300, or 1000 mg/kg-day DBS in

an unspecified vehicle on GD 7-19 and sacrificed on GD 29 (Pfizer, 2014e). At the high dose, three does were sacrificed moribund, and two additional does were sacrificed after showing evidence of aborted litters. Food consumption and feces production were also decreased at the high dose. The surviving high-dose animals exhibited decreased mean body weight (not weight gain) beginning on GD 13. There was no effect on body weight in the low or mid doses. Aside from the full litter abortions at the high dose, there were no effects on cesarean section data. There were two malformations at the high dose (lumbar vertebra-hemivertebra and thoracic centrum-fused) and several skeletal variations (bent hyoid, interparietal and sternebra incomplete ossification, sternebra bipartitie ossification, unossified caudal vertebra, additional ossification site of cervical centrum), but the malformations and variations were within historical control values, and FDA apparently did not consider them treatment-related. FDA identified the mid dose of 300 mg/kg-day as the maternal NOAEL, based on reductions in body weight and food consumption and moribund sacrifice, and as a developmental NOAEL, based on aborted litters at 1000 mg/kg-day. FDA considered it most likely that the aborted litters were secondary to maternal toxicity.

5.6 Genotoxicity

DBS was negative for genotoxicity in all of the available studies, although several were not fully documented. DBS was negative in the Ames assay in the presence and absence of S9 activation, up to 3.6 mg/plate in TA1535, TA100, TA1537, TA100, and TA98 (Wild et al., 1983), although the study is limited by the absence of reported data on solvent controls. DBS was also negative for bacterial mutation +/-S9 activation in *Salmonella* strains TA97, TA98, TA100, TA 102, and *Escherichia coli* WP2/pKM101, in testing up to the limit dose (Hachiya and Takizawa, 1994, as cited by ECHA, 2018b). DBS was also negative in the Basc test for sex-linked recessive lethal mutations in *Drosophila melanogaster*, at a dose up to 19 mM.

No *in vitro* chromosome aberration tests with DBS were located. However, DBS was negative in the mouse micronucleus assay at a dose up to 2829 mg/kg, with sacrifice 30 hours after treatment (Wild et al., 1983). The dosing route was not explicitly stated, but ECHA (2018b) listed it as intraperitoneal, which is typical for this assay type.

5.7 Mechanistic Studies

In light of the endocrine-activity of the phthalates that DBS may replace, several studies investigated the estrogenic and androgenic potential of DBS. Hashimoto and Nakamura (2004) evaluated the estrogenic potential of DBS in the e-screen assay. In this assay, breast-tumor derived MCF-7 cells are exposed to the test chemical, and the potential of the chemical to mimic growth stimulation by estradiol is evaluated. DBS in ethanol did not stimulate the growth of the MCF-7 cells, indicating that it is negative for estrogenic activity. Bisphenol A produced the expected stimulation at multiple concentrations. ECHA (2018b) considered the study to have "major methodological deficiencies," but it appears that the key concern was that the method had not been sufficiently validated.

In another study by the same group (Nishijima et al., 2002), DBS was evaluated in three *in vitro* tests for estrogenic activity. DBS was negative +/-S9 in a yeast strain Y190 using reporter genes, negative for estrogen receptor binding, and negative in the MCF-7 e-screen. Rather than showing results for the positive controls, the authors showed the results relative to the positive control, and so it is challenging to determine whether the data are different from those of Hashimoto and Nakamura (2004). As for the previous study, ECHA (2018b) considered the study to have "major methodological deficiencies," but it appears that the key concern was that the methods had not been sufficiently validated.

In another study from the same group, which was available only in Japanese, but with an English abstract and figure and table legends, Ohta et al. (2003) evaluated DBS and other phthalate substitutes for estrogenic and androgenic activity. DBS was inactive in *in vitro* assays for binding to the human estrogen receptor (hER-α and hER-β) and the rat androgen receptor. The expected receptor binding was seen with both estradiol and bisphenol A (estrogen receptor) and with testosterone and *p,p'*-dichlorodiphenyldichloroethylene (DDE) (androgen receptor). In the uterotrophic assay, DBS at 0.5 or 500 mg/kg (exposure route not available) did not stimulate increased uterine weight, and there was no evidence of hyperplasia of the uterine endometrium or cornification of vaginal mucosa; the expected increases were observed with the estradiol positive control. Interpretation of this study is limited by the absence of additional experimental details in English, but the data support the conclusion that DBS lacks estrogenic or androgenic activity. It is not clear if this study reports any novel data not presented by Nishijima et al. (2002) or Hashimoto and Nakamura (2004). Although these three studies used unvalidated methods, the overall results are consistent with those from *in vivo* studies that DBS does not have anti-estrogenic or anti-androgenic activity.

In an *in vitro* study, Mochida et al. (1996) found that DBS was substantially less cytotoxic than acetyl tributyl citrate (ATBC) to human KB, monkey Vero and dog MDCK cell lines. The ID_{50} (concentration that reduced cell growth to 50% of control culture during a 72-hour exposure) was at least 20-fold higher (lower toxicity) for DBS than ATBC for each cell line.

5.8 Mode of Action (MOA)

In light of the very low toxicity seen with DBS and the few reported adverse effects, no MOA evaluation is possible. However, both *in vitro* (Nishijima et al., 2002; Ohta et al., 2003; Hashimoto and Nakamura, 2004) and *in vivo* (Pfizer 2014c, as cited by FDA, 2014) data support the conclusion that DBS does not have anti-estrogenic or anti-androgenic activity. Similarly, the weight of the evidence is that DBS does not cause gene mutations or chromosome damage (Wild et al., 1983; Hachiya and Takizawa, 1994, as cited by ECHA, 2018b).

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

The toxicity of DBS is very low, and adverse effects have been seen only in developmental toxicity studies. There was no evidence of any systemic toxicity in male and female rats or dogs exposed for 26 weeks in GLP compliant and ICH compliant studies conducted up to 1000

mg/kg-day (Pfizer, 2014a, 2014b, as cited by FDA, 2014). There was also no evidence of systemic toxicity in male and female rats exposed for 1 years to doses up to 862.5 mg/kg-day or for 2 years to doses up to 4312 mg/kg-day in the diet (Smith, 1953), although these chronic studies had small sample sizes, limited histopathology, and were not conducted according to modern test methods.

There was no evidence that DBS affects the reproductive system, although there are several uncertainties, as noted in Section 5.10.

DBS did not cause developmental toxicity in rats gavaged at doses up to 1000 mg/kg-day (Pfizer, 2014d, as cited by FDA, 2014), although decreased pup weight was reported at the higher dose of 4312 mg/kg-day in a dietary study, in the absence of maternal toxicity (Smith, 1953). Full litter abortions were reported in rabbits gavaged with 1000 mg/kg-day (Pfizer, 2014e), although FDA considered it likely that the abortions were secondary to maternal toxicity. No other treatment-related developmental effects were reported.

The weight of evidence is that DBS is not genotoxic. It was negative for gene mutations in bacteria (Wild et al., 1983; Hachiya and Takizawa, 1994, as cited by ECHA, 2018b) and for micronuclei *in vivo* (Wild et al., 1983).

In the one available chronic study, DBS was negative for carcinogenicity in rats at a dietary dose of 4312 mg/kg-day (Smith, 1953). However, this study was conducted prior to modern testing methods, and has several limitations, as noted in Section 5.10.

5.10 Uncertainties and Data Gaps

Database:

All of the key study types are available for DBS for the oral route, using modern testing methods, although several of the studies have limitations, based on the available information. Systemic toxicity studies conducted up to a limit dose of 1000 mg/kg-day and lasting 26 weeks (greater than subchronic for a rat) are available for the rat (Pfizer, 2014a, as cited by FDA, 2014), and the dog (Pfizer, 2014b, as cited by FDA, 2014). These studies included a wide array of endpoints. A one-generation reproductive study is also available (Pfizer, 2014c, as cited by FDA, 2014), as well as developmental studies in rats (Pfizer, 2014d, as cited by FDA, 2014) and in rabbits (Pfizer, 2014e, as cited by FDA, 2014). Inhalation studies are lacking. Although several acute inhalation studies are available, they did not adequately characterize the actual exposure concentration (Union Carbide, 1983, as cited by BIBRA, 1998; Astapova et al., 1990, as cited by ECHA, 2018b, BIBRA, 1998, and RTECS, 2018), or are based on surrogates (Anonymous, 1989a, Anonymous 1998, both as cited by ECHA, 2018b). Study details are generally lacking.

Data on dermal irritation and sensitization potential of DBS are available from both animal (de Groot et al., 1991, and as cited by BIBRA, 1998; Anonymous, 1976, as cited by ECHA, 2018b; Mallette and Von Haam, 1952, as cited by ATSDR, 1995) and human (Mallette and Von Haam

1952, as cited by BIBRA, 1998; ATSDR, 1995; Askarova and Muryseva 1975, as cited by ATSDR, 1995) studies, although study details are often lacking.

An additional data gap is that the available standard toxicity studies were either conducted prior to modern test methods, or are available only based on the summaries in secondary sources.

Hazard:

Sensitization: There is some indication that DBS may have sensitizing potential, based on an occupational study reporting sensitization of workers, but details are limited (Askarova and Muryseva, 1975, as cited by ATSDR, 1995). Skin sensitization was not reported in a test in rabbits, but experimental details are also limited in this study (Mallette and Von Haam, 1952). In addition, the rabbit is not the preferred species for sensitization testing under modern test methods. A guideline-compliant study (guinea pig maximization test) was negative with the structurally related compound dibutyl adipate (DBA) (Anonymous, 1989b, as cited by ECHA, 2018b). Based on the limited data, DBS may be a sensitizer, but no definitive conclusion is possible.

Reproductive: A key limitation is that existing studies either were not conducted according to modern methods (Smith, 1953), or did not expose the males for the full spermatogenic cycle prior to mating (Pfizer, 2014c, as cited by FDA, 2014). In addition, it is unclear whether complete histopathology of the reproductive tract was conducted, even in the guideline study (Pfizer, 2014c, as cited by FDA, 2014). Finally, recently-added endpoints reflecting endocrine disruption (e.g., estrus cycle length, anogenital distance) were not investigated.

Carcinogenicity: DBS is not expected to be carcinogenic, based on the negative genotoxicity findings. However, it is also noted that the single chronic study (Smith, 1953) did not use an adequate number of animals, and did not evaluate the full array of tissues covered by modern testing methods.

Table 2. Summary of NOAELs/LOAELs Identified for DBS by Organ System

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified[4]	Toxicological Basis	Comments
Oral					
Crl:WI(Han) rat (M and F) (15/sex/dose) Pfizer, 2014a, as cited by FDA, 2014	26 weeks Gavage in a proprietary water-based vehicle 0, 100, 300, or 1000 mg/kg-day	Systemic	NOAEL = 1000 (M, F) No LOAEL	No adverse effects observed	GLP and ICH M3(R2) compliant No effect on body weight, food consumption, ophthalmoscopy, hematology, urinalysis, clinical chemistry, organ weight or histopathology
Beagle dog (M and F) (4/sex/dose) Pfizer, 2014b, as cited by FDA, 2014	26 weeks Gavage in a proprietary water-based vehicle 0, 100, 300, or 1000 mg/kg-day	Systemic	NOAEL = 1000 (M, F) No LOAEL	No adverse effects observed	GLP and ICH M3(R2) compliant No effect on body weight, food consumption, ophthalmoscopy, electrocardiogram (ECG), hematology, urinalysis, clinical chemistry, organ weight or histopathology
Sprague Dawley rat 10/dose (M) Smith (1953)	1 year Diet	Systemic	NOAEL = 862.5 (M) No LOAEL	No adverse effects observed	Dose calculated using a strain-specific food factor of 0.069; BIBRA (1998) used a food factor of 0.05.

[4] All effect levels as identified by the authors of this assessment. Effect levels identified by previous assessments are in the comments column

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified[4]	Toxicological Basis	Comments
	0, 0.01, 0.05, 0.25, 1.25% Approximately 0, 6.9, 34.5, 172.5, 862.5 mg/kg-day				Study is limited by the small sample size and limited reporting. Histopathology evaluated for the lungs, heart, liver, spleen, adrenals, kidneys, stomach, small intestine, thyroid and brain
Sprague Dawley rat 16/dose; 32 controls (M) Smith (1953)	2 years Diet 0, 0.01, 0.05, 0.25, 1.25, 6.25% Approximately 0, 6.9, 34.5, 172.5, 862.5, 4312 mg/kg-day	Systemic	NOAEL = 4312 (M) No LOAEL	No adverse effects observed	Dose calculated using a food factor of 0.069; BIBRA (1998) used a food factor of 0.05. Study is limited by the small sample size and limited reporting. Histopathology evaluated for the lungs, heart, liver, spleen, adrenals, kidneys, stomach, small intestine, thyroid and brain
Crl:CD(SD) rat (M and F) 20/sex/dose Pfizer 2014c, as cited by FDA, 2014	1 generation beginning at least 28 d prior to mating (M) or at least 14 d prior to mating through GD 7 (F)	Systemic	NOAEL = 1000 (M, F) No LOAEL	No adverse effects observed	GLP and ICH M3(R2) compliant No mention in summary of whether histopathology of reproductive organs sperm parameters, estrus cycle evaluated, and dosing of males prior to mating too short to include entire spermatogenic cycle
		Reproductive	NOAEL = 1000 (M, F) No LOAEL	No adverse effects observed	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified[4]	Toxicological Basis	Comments
	Gavage in a proprietary water-based vehicle 0, 100, 300, 1000 mg/kg-day				
Sprague Dawley rat 20/sex/dose; 10/sex for controls (M and F) Smith (1953)	10 weeks prior to mating through PND 42 Diet 0, 6.25% Approximately 0, 4312.5 mg/kg-day	Systemic	NOAEL = 4312 (M, F) No LOAEL	No adverse effects observed	Dose estimated based on a food factor of 0.069. Study limited by incomplete reporting. Histopathology apparently not evaluated, and control group size is small
		Reproductive	NOAEL = 4312 (M, F) No LOAEL	No adverse effects observed	
		Developmental	No NOAEL LOAEL = 4312 to the dam; 9188 to the pups (M, F)	Decrease in pup body weight and weight gain	
Pregnant Sprague-Dawley rat (F) 22/dose Pfizer 2014d, as cited by FDA, 2014	GD 6-17 Gavage in a proprietary water-based vehicle 0, 100, 300, 1000 mg/kg-day	Maternal	NOAEL = 1000 No LOAEL	No adverse effects observed	GLP and ICH M3(R2) compliant
		Developmental	NOAEL = 1000 No LOAEL	No adverse effects observed	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified[4]	Toxicological Basis	Comments
Pregnant Hra: (NZW)SPF rabbit (F) 22/dose Pfizer 2014e, as cited by FDA, 2014	GD 7-19 Gavage in a proprietary water-based vehicle 0, 100, 300, 1000 mg/kg-day	Maternal	NOAEL = 300 LOAEL = 1000	Lethality, full litter abortions	GLP and ICH M3(R2) compliant FDA considered the abortions probably secondary to maternal toxicity. Two malformations and several variations were observed at the high dose, but these were within the historical control range and FDA did not consider them to be treatment-related.
		Developmental	NOAEL = 300 LOAEL = 1000	Full litter abortions	

6 Exposure

The use of DBS in consumer products has been described in Section 3 of this report. The general population may be exposed to DBS via dermal contact with consumer products (including cosmetics); via mouthing of products (e.g., children's toys); by the ingestion of food, beverages, or medications containing this compound; by ingestion of foods stored in packaging containing DBS; and, by ingestion and dermal contact with contaminated household water supplies.

Abe et al. (2012) measured plasticizers in 101 samples of PVC toys on the Japanese market. They found DBS in 7% of the samples ("designated toys"[5]) with a mean concentration (detected samples only) of 0.07%, and in 4% of the samples ("not-designated toys") with a mean concentration (detected samples only) of 0.03%.

DBS is used as a component of adhesives used in food packaging and as a food additive (HSDB, 2018). DBS was detected in polyvinylidene chloride (PVCD) wrapping films (Kawamura et al., 1999; as cited by Bui et al., 2016) and in gaskets for lids of glass jars (Rothenbacher and Schwack, 2010). Motegi et al. (1978) studied migration of DBS from PVDC film into several fatty food simulants and calculated total migration. Migration of DBS was 45-290 µg/g PVDC (when heated at 90° C for 90 minutes) in the model fatty foods and 8.3 times greater in n-heptane.

Castle et al. (1988) surveyed samples of foods purchased from supermarkets in the United Kingdom and measured levels of DBS ranging from 76 mg/kg to 137 mg/kg in processed cheese and cooked meat packaged in plastic. ATSDR (1995) reported that the containers in this study contained from 3.5% to 4.1% DBS. Bui et al. (2016) reported that Tsumura et al. (2002) did not detect DBS in Japanese food.

DBS was detected in a sample of finished water from an advanced waste treatment plant in Lake Tahoe, California, but the concentration was not reported (U.S EPA 1984a, 1984b; as cited by ATSDR, 1995). The enteric coating on medications have also been reported as a potential source of exposure to DBS (Hauser et al., 2004).

NIOSH (1983, as cited by HSDB, 2018) reported that occupational exposure to DBS may occur through inhalation or dermal contact with the compound where it is produced or used, and reports an estimate of 4826 workers potentially exposed in the U.S.

[5] Japanese publication with abstract and tables only in English. We assumed "designated" refers to those toy types that are defined as "designated toys" in Article 78 of the Ordinance for Enforcement of the Food Sanitation Act (revised in March 2008) (https://www.jetro.go.jp/en/reports/regulations/pdf/foodext201112e.pdf). "Designated toys" include those toys intended to come into direct contact with an infant's mouth, infant jewelry, decal sticker toys, rolly-polies, masks, origami, rattles, intellectual development facilitating toys, wooden blocks, toy telephones, toy animals, dolls, clay, toy vehicles, balloons, toy building bricks, balls, housekeeping toys, and toys to be played with in combination to those types of toys listed.

7 Discussion

7.1 Toxicity Under FHSA

Animal data were sufficient to support the conclusion that **DBS does not fit the designation of acutely toxic under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A))** following single oral exposures. Acute LD_{50} values for DBS in rats were >5000 mg/kg for oral exposure (Anonymous, 1976, as cited by ECHA, 2018b; Smith, 1953). No lethality was seen in an acute dermal test of DBS in rabbits, but the dose tested was not reported (Mallette and von Haam, 1952). DBS has not been tested to high enough concentrations in air to determine whether it is toxic via the inhalation route.

DBS was not irritating or very minimally irritating to the skin. It was not irritating when applied to the skin of volunteers as a neat liquid (Mallette and Von Haam 1952, as cited by BIBRA, 1998) or as a 10% solution in petrolatum (de Groot et al., 1991, and as cited by BIBRA, 1998). Very minimal skin irritation was observed when undiluted DBS was applied to the shaved and abraded skin of rabbits in a study generally conducted according to guidelines (Anonymous, 1976, as cited by ECHA, 2018b). The only evidence of irritation was erythema (grade 1 of 4) in one rabbit at 24 hours. The authors concluded that DBS was not irritating.

The eye irritation potential of DBS is also low. Some eye redness (score of 1 on a scale of 3 or 4) that resolved in less than 72 hours was seen in rabbits in a guideline-compliant eye irritation study. The study authors concluded that DBS was not irritating to the eye.

There is some indication that DBS may be a sensitizer, but no definitive conclusion is possible. Sensitization was reported in an occupational study where exposure was via an unspecified route at unspecified levels (Askarova and Muryseva, 1975, as cited by ATSDR, 1995), but not in a skin sensitization test in rabbits, for which experimental details are also limited (Mallette and Von Haam, 1952). No sensitization test with DBS has been conducted using modern test methods, but a guideline-compliant study (guinea pig maximization test) was negative with the structurally related compound dibutyl adipate (DBA) (Anonymous, 1989b, as cited by ECHA, 2018b).

The systemic toxicity of DBS following repeated dosing is very low; systemic toxic effects have not yet been reported in reliable studies conducted up to the limit dose (Pfizer, 2014a, 2014b, as cited by FDA, 2014).

DBS has been tested for reproductive toxicity in rats up to 1000 mg/kg-day by gavage, under ICH guidelines (Pfizer, 2014c, as cited by FDA 2014). It was also tested up 4312 mg/kg-day in a dietary study in rats that included longer-duration exposure, but was conducted prior to modern test methods (Smith, 1953). Neither study found any evidence of reproductive toxicity, although evaluation of the spermatogenic cycle and some endocrine-related endpoints was not according

to modern standards in either study. However, DBS was negative in several *in vitro* tests for estrogenic and androgenic activity (Nishijima et al., 2002; Ohta et al., 2003; Hashimoto and Nakamura, 2004).

DBS is not teratogenic, but high doses can cause developmental toxicity. DBS caused decreased pup weight following exposure *in utero* and after weaning at dietary concentrations resulting in adult exposure to 4132 mg/kg-day and weanling exposure to 9188 mg/kg-day (Smith et al., 1953). Full litter abortions that were considered secondary to maternal toxicity were observed in rabbits gavaged with 1000 mg/kg-day on GD 7-19 (Pfizer 2014e, as cited by FDA, 2014). Malformations and variations observed in the rabbit study were not considered by FDA (2014) to be treatment related.

The weight of evidence is that DBS does not cause gene mutations or chromosome damage (Wild et al., 1983; Hachiya and Takizawa, 1994, as cited by ECHA, 2018b).

In the one available chronic study, DBS was negative for carcinogenicity in rats at a dietary dose of 4312 mg/kg-day (Smith, 1953). However, this study was conducted prior to modern testing methods, and has several limitations.

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APPENDIX 1

Search Terms Used

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

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

APPENDIX 2

Explanation of Physico-chemical Parameters

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

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

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

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