



**CPSC Staff Statement on University of Cincinnati Report
“Toxicity Review for Dibutyl Adipate (DBA) and Di-isobutyl
Adipate (DiBA)”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 DBA and DiBA follows. Based on the research conducted by the University of Cincinnati, the animal data were sufficient to support the conclusion that DBA does not fit the designation of acutely toxic under the FHSA following dermal exposure. However, the data are insufficient to determine whether DBA fits the designation of acutely toxic under the FHSA following single oral or inhalation exposures. The data are insufficient to determine whether DiBA fits the designation of acutely toxic under the FHSA following single oral, dermal, or inhalation exposures.

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 and Diisobutyl Adipate
(DBA; DiBA)**

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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 adipate (DBA) and di-isobutyl adipate (DiBA).

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

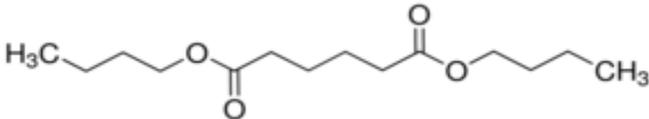
Searches were conducted for studies indexed to PubMed and Toxline databases from all dates to the the date of the search (July, 2018). Other databases and websites were also used to identify additional key information, particularly authoritative reviews. Authoritative reviews for general toxicity and physicochemical information were identified in the following databases using the CAS number for DBA/DiBA 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 of DBA

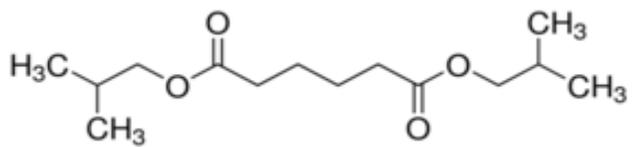
Chemical Name	Dibutyl Adipate
Synonyms	Dibutyl hexanedioate, Butyl adipate, Di-n-butyl adipate, Hexanedioic acid, Dibutyl ester
CAS Number	105-99-7
Structure	
Chemical Formula	C ₁₄ H ₂₆ O ₄
Molecular Weight	258.0358 g/mol
Physical State	Liquid
Color	Colorless
Melting Point	-38°C
Boiling Point	183°C (OECD, 1996)
Vapor Pressure	1.07 x 10 ⁻³ mm Hg (U.S. EPA, 2018a)
Water Solubility	3.016 x 10 ⁻⁴ mol/L (U.S. EPA, 2018a)
Log Kow	4.017 (OECD, 1996)
Log Koc¹	1.23 x 10 ³ L/kg (U.S. EPA, 2018a)
Henry's Law	1.01 x 10 ⁻⁷ (U.S. EPA, 2018a)
Flashpoint	113°C

BCF	27.0 (predicted average) (U.S. EPA, 2018a)
Density	0.96 g/mL
Source	PubChem (2018a), 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.

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

Table 2: Physical-Chemical Characteristics of DiBA

Chemical Name	Diisobutyl Adipate
Synonyms	Adipic acid Bis(2-Methylpropyl)ester, Diisobutyl ester, Adipic Acid, Isobutyl Adipate, Hexanedioic acid (HSDB, 2019)
CAS Number	141-04-8
Structure	
Chemical Formula	$C_{14}H_{26}O_4$
Molecular Weight	258.036 g/mol
Physical State	Liquid
Color	Colorless
Melting Point	-20°C
Boiling Point	278-280°C
Vapor Pressure	5.063×10^{-3} mm Hg (ChemID, 2018)
Water Solubility	18.08 mg/L (ChemID, 2018)
Log Kow	4.0190 (ChemID, 2018).
Log Koc¹	608 L/kg (U.S. EPA, 2018b)
Henry's Law	9.71×10^{-8} atm-m ² /mole (U.S. EPA, 2018b)
Flashpoint	123 - 130°C (U.S. EPA, 2018b)
Density	0.9534 g/cm ³ at 19°C
BCF	34.6 (predicted average) (U.S. EPA, 2018b)
Source	PubChem (2018b), 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.

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

ECHA (2018c) included several studies of di(2-ethylhexyl)adipate (DEHA) in the DBA dossier, using a read-across category approach. This has the advantage that there is an extensive database for DEHA, and DEHA shares the adipate core with DBA and DiBA. However, because toxicity is often due to the functional groups in a chemical (including branching), the toxicity of DBA and DiBA may more closely resemble that of dibutyl sebacate (DBS), than that of DEHA. In addition, it is noted that ECHA (2018c) used a category approach, based on DEHA and other related chemicals, rather than using DEHA as a surrogate. Therefore, the DEHA (and DBS) studies are not summarized in this report.

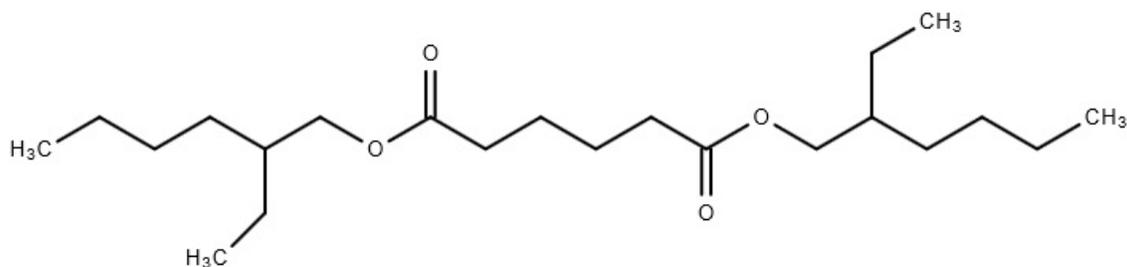


Figure 1. Structure of di(2-ethylhexyl)adipate (DEHA)

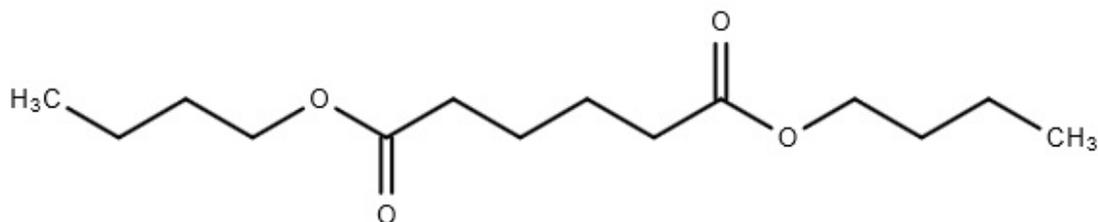


Figure 2. Structure of dibutyl sebacate (DBS)

3 Manufacture, Supply, and Use

Manufacture and Supply

DBA is a high production volume chemical in both the U.S. and Europe (U.S. EPA, 2018c; OECD, 2018). The overall amount produced and/or imported in the European Economic Area is 100+ tons per year (ECHA, 2018a). Production volume in Japan was less than 100 tons per year from 1987-1992 (OECD, 1996). DBA is produced in a closed system and is used mainly as a plasticizer for resins (OECD, 1996).

DiBA is a high production volume chemical in the U.S., with manufacture and/or imports reported between 100,000 and 500,000 pounds (50 – 250 tons) per year for 2015 (U.S. EPA,

2018d). The overall amount produced and/or imported in the European Economic Area is 10 - 100 tons per year (ECHA, 2018b).

Use

DBA is used in the manufacturing of lubricants, adhesives, polishes, cleaning products, and plant protection products (ECHA, 2018a). It is also used in washing machine liquids, automotive care products, paints and coatings, adhesives, fragrances, and air fresheners (ECHA, 2018a). It is proposed by manufacturers of plasticizers as an alternative for DBP (Maag et al., 2010). Uses include polyurethane foam sealants, nitrocellulose paints, resins, and consumer floor wax (Maag et al., 2010; OECD, 1996; Bui et al., 2016). DBA is an indirect food additive for use only as a component of adhesives (HSDB, 2018) and is found in food-grade PVDC packaging films (Wei et al., 2009). In cosmetics, DBA functions as a plasticizer, skin-conditioning agent, and as a solvent (Andersen, 2006).

DiBA is a widely used plasticizer to improve the extensibility, elasticity, and working ability of polyvinyl chloride (Guo et al, 2010). DiBA is used in “soft” and “PVC” toys and childcare articles (FCPSA, 2008, as cited by Maag et al, 2010; Abe et al., 2012). DiBA is found in a number of hair styling products (Household Products Database, 2018).

DiBA is also used as a solvent (U.S. EPA, 2018e), in coating products (ECHA, 2018b), and as a flavoring agent (JECFA, 2010, as cited by PubChem, 2018). Subedi et al. (2017) found DiBA in dust samples in homes, childcare facilities, and salons, and hypothesized that the higher levels of DiBA in salon dust may be due to higher cosmetic use in that environment (Subedi, 2017).

4 Toxicokinetics

No studies designed to evaluate the toxicokinetics of DBA or DiBA were located. However, the observation of toxicity following oral exposure to DBA or DiBA (MHW, 1996a, as cited by OECD, 1996, ECHA, 2018c; MHW, 1996, as cited by ECHA, 2018d), shows that oral absorption occurs to a meaningful degree. The data are weaker for the dermal and inhalation routes, but there are suggestive data of DBA systemic toxicity from dermal exposure (Mellon Institute of Industrial Research 1950, as cited by Andersen, 2006) and inhalation exposure (Astapova et al., 1990, as cited by ECHA, 2018c). The studies via the inhalation and dermal routes were not conducted according to modern testing methods and/or were poorly documented, but the results are supportive of the conclusion that meaningful absorption can also occur via these routes.

No studies were located on dermal or inhalation toxicity for DiBA, so it is not possible to infer anything about absorption via these routes for DiBA.

No data were located on the metabolism of DBA or DiBA, but part of a likely pathway can be inferred based on the structure, which suggests hydrolysis of the ester linkage. DBA does not hydrolyze at pH 4, but does spontaneously hydrolyze at pH ≥ 7 in water (MITI, Japan, 1994, as

cited by OECD, 1996). The half-life was 1850 days at pH 7 and 7.3 days at pH 9, indicating base hydrolysis. The slow hydrolysis at pH 7 suggests that hydrolysis may not occur at a meaningful rate in the blood or tissue. However, although there was no hydrolysis at pH 4, data were not provided for hydrolysis under the more acidic conditions of the stomach, where hydrolysis can be presumed to be likely. The hydrolysis products would be the mono adipate, followed by production of butanol (DBA) or isobutanol (DiBA) and adipic acid. However, no information is available on the kinetics of these presumed processes, and whether they would be relevant to DBA or DiBA toxicity.

5 Hazard Information

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

DBA

Smyth and Carpenter (1944, as cited by ECHA, 2018c; also reported by Smyth et al., 1951) reported an LD₅₀ of 12,900 mg/kg (20% dispersion) in male Wistar rats tested in the up and down method (groups of 6) and observed for mortality for 14 days. Andersen (2006, citing the Mellon Institute of Industrial Research, 1950) reported an oral LD₅₀ in rats of 11,260 mg/kg for a 20% dispersion in Tergitol 7. RTECS (2018, citing Frear, 1976) reported an LD₅₀ of 12,900 mg/kg in rats with no further details, while OECD (1996) cited the same secondary reference (Frear, 1976) as providing an oral LD₅₀ of 1290 mg/kg in rats (no further information provided). Given that most of the references reported the higher LD₅₀, this suggests that the report by OECD may be a typographical error. Furthermore, since Smyth and colleagues were at Carnegie Mellon, it is likely that the different reports reflect the same or closely-related experimental studies. It is noted, however, that this study(s) was done prior to modern testing methods. Prostration and narcosis were reported “at greater doses” in the Mellon Institute (1950, as cited by Andersen, 2006) study. Liver, kidney and gastrointestinal tract congestion were reported at necropsy.

In contrast to the very high LD₅₀ from the work in the 1950’s, a more modern study reported an LD₅₀ value that was lower by almost an order of magnitude. Cognis Deutschland GmbH & Co (2002, as cited by Andersen, 2006) treated groups of 10 male Wistar rats with undiluted DBA or DBA diluted in olive oil (dilution factor not available), and determined an LD₅₀ of 1520 mg/kg. It is not known whether the difference in LD₅₀ reflects the use of a modern dosing protocol, the difference in vehicle, or something else.

Astapova et al. (1990, as cited by RTECS, 2018; ECHA, 2018c) listed an oral LD₅₀ of ~16,800 mg/kg for mice, and 16,920 mg/kg for rats. ECHA (2018c) disregarded these results due to major methodological deficiencies. The nature of the deficiencies is not entirely clear, but may be because the cause of death is listed as the lack of oxygen in the microcirculation. Further details were not available.

DiBA

An oral LD₅₀ of 12.1 mL/kg (11,500 mg/kg, based on a density of 0.95 g/mL) was identified in rats (Gloxhuber, 1969, as cited by ECHA, 2018d). No other study details were provided. An oral LD₅₀ of 12.3 mL/kg (11,690 mg/kg, based on a density of 0.95 g/mL) in guinea pigs was reported by RTECS (2018, citing German Offenlegungsschrift Patent, undated). No other study details were provided. In a more recent study, an LD₅₀ of 1290 mg/kg was reported in male and female rats (strain unspecified) (Anonymous, 1996, as cited by ECHA, 2018d). No other study details were provided¹.

In an unpublished study, Moreno et al. (1980, as cited by WHO, 2011) reported an LD₅₀ in rats as >5000 mg/kg. No other details were provided.

5.1.2 Acute Dermal Toxicity

Smyth and Carpenter (1944, as cited by ECHA, 2018c; also reported by Smyth et al., 1951, Andersen, 2006) reported a dermal LD₅₀ for DBA in rabbits of 20 mL/kg (about 19,000 mg/kg). Study details are limited, but 6 rabbits (strain unspecified) were treated with undiluted DBA or an unspecified series of doses differing by factors of 10 under occlusion with no test vehicle, and were observed for 14 days (ECHA, 2018c).

No acute dermal data were identified for DiBA.

5.1.3 Acute Inhalation Toxicity

The acute inhalation data for DBA are limited to several studies conducted using air saturated or nearly-saturated with DBA. These studies do not meet modern testing criteria.

Smyth et al. (1951, and as cited by Andersen, 2006) reported no deaths in a study of six male albino rabbits exposed to air “substantially saturated” with DBA for 8 hours. Similarly, no deaths were reported when an unspecified number of mice and rats were exposed to 17 mg/m³ for 2 hours and 4 hours, respectively. The exposure concentration was generated based on a saturated atmosphere at 50°C and was reported to have been verified analytically (Astapova et al., 1990, as cited by ECHA, 2018c, RTECS, 2018). Signs of toxicity were reported as failure of redox processes, failure in liver and kidney function, and changes in hematological and immunological parameters.

ECHA (2018c) also reported on read-across from high-quality inhalation toxicity studies with other adipates, for which the acute inhalation LC₅₀s were 3000 mg/m³ or higher.

No data on acute inhalation toxicity were identified for DiBA.

5.1.4 Irritation/Sensitization

¹ There is some possibility that this may be misreporting of the LD₅₀ of 12,900 by Smyth et al. (1951) for DBA, but this possibility cannot be investigated in the absence of additional citation details in ECHA (2018d).

DBA, skin irritation

Two studies are available of dermal irritation testing with volunteers (Cognis Deutschland GmbH and Co., 2002, as cited by Andersen, 2006). In the first study, undiluted DBA (unspecified volume) was applied in a 24-hour patch test to the skin of 10 volunteers (age, sex, race not reported). No skin irritation was reported at 24 or 48 hours; additional details were not available. In the second study, an unspecified volume of DBA at 20% in alcohol was applied to the skin of 18 volunteers using Finn chambers for 24 hours. Four people had slight reactions (not further described).

In an OECD Guideline 404 study, three Small White Russia ChbbSPF rabbits were exposed for 4 hours on a 6 cm² area of the dorsal and lateral trunk under semi-occluded conditions to 0.5 mL of undiluted DBA² (Anonymous, 1989, as cited by ECHA, 2018c). At 1 hour of exposure, grade 2 erythema and grade 1 edema (both on a scale of 4) were seen on all exposed animals. At 6 days, one rabbit showed scaling and another exhibited eschar formation. All symptoms were reversible within 8 days. ECHA (2018c) classified DBA as irritating.

One study was listed as ‘unassignable’ quality by ECHA due to only the abstract being available. This was an *in vivo* skin irritation study in 5 hairless mice exposed to DBA twice daily for 14 days (no vehicle, no controls). The study conclusion was “no infectious symptoms were observed” (Anonymous, 1970, as cited by ECHA, 2018c). It was not clear why the results addressed “infectious symptoms” rather than irritation.

Andersen (2006) summarized several additional dermal irritation studies. Two of these studies were conducted by Cognis Deutschland GmbH & Co, (2002). In the first, 10% DBA in acetone was applied to the ears of five hairless mice once a day for 10 days. No macroscopic effects were observed on the ears. In the second study, DBA (apparently undiluted) was applied to the backs of hairless mice twice a day for 14 days, with no dermal reactions reported.

Andersen (2006) also reported on several studies conducted prior to the development of modern test methods. In the first study, three rabbits (strain not specified) were exposed to cloth bands impregnated with 1.0 g/ft² DBA on a 0.5 ft² clipped area of the trunk for (presumably consecutive) 3-day intervals over three weeks (total of 7 applications) (cited as Mellon Institute of Industrial Research, 1950). After the first 3-day exposure, two rabbits exhibited moderate erythema; however, no signs of irritation were evident following the three-week exposure period. In the second study, five rabbits (strain not specified) were exposed to cloth bands impregnated with 2.0, 4.0, or 8.0 g/ft² DBA on the clipped trunk (cited as Mellon Institute of Industrial Research, 1951). New bands were applied twice a week over a 21-day test period (total of 6 applications). No progressive damage to the skin was observed. However, in a related experiment from these same researchers, five albino rabbits directly exposed to 0.01 mL DBA on clipped skin 8 times over a 4-hour test period exhibited moderate erythema after 24 hours (cited as Mellon Institute of Industrial Research, 1951). Andersen (2006) did not address the reason for the difference in results among the different studies, but it is noted that the third study followed the modern testing approach of applying the material directly to the animal skin, while the first

² Referred to by its German name, adipinsäure-di-n-butylester.

two studies applied the material to the cloth, and so the actual amount in contact with the skin is unknown.

In another study documented in the same report (cited as Mellon Institute of Industrial Research, 1951), 0.025 mL DBA was applied to three rabbits on intact and abraded abdomens for 3-hour intervals, 3 times a day, for 3 days. All rabbits showed erythema and/or capillary injection during the study and desquamation 3 days following the last application.

Smyth et al. (1951, as further described by Andersen, 2006) applied 0.01 mL of DBA to the clipped belly of albino rabbits (no other data provided). After 24 hours, the primary irritation score reported was 2 (on a scale of 8).

DBA, eye irritation

DBA was instilled into one eye each of two male volunteers at 0.1% in paraffin oil (Cognis Deutschland GmbH and Co., 2002, as cited by Andersen, 2006). No conjunctival reactions were observed within 24 hours.

In an OECD Guideline 405 study, 0.1 mL of neat DBA³ was instilled into one eye of Small White Russia Chbb-SPF rabbits for 72 hours, after which the eye was rinsed with saline (Anonymous, 1989, as cited by ECHA, 2018c). No irritation of the cornea or iris was reported, but grade 1 conjunctival injection (on a scale of 3) was seen in two of three animals; this irritation was reversed after 24 hours. DBA was considered “not irritating” to the eyes in this study.

Cognis Deutschland GmbH & Co. (2002, as cited by Andersen, 2006) conducted two eye irritation studies in rabbits. When undiluted DBA (volume not specified) was instilled into the eyes of two New Zealand rabbits, slight corneal irritation was observed, and resolved “after a few days.” In another study, 0.1 mL of DBA (at 0.1% in olive oil) was instilled into the eyes of two New Zealand rabbits without rinsing. Observations at 2, 6, and 24 hours after application reported no reactions of the cornea, iris, or conjunctivae.

Smyth et al. (1951) instilled neat DBA (volume not available) into the conjunctival sac of an unspecified strain of rabbits. The eye irritation score was 1 (on a scale of 10). Further details were not available.

ECHA (2018c) also reported on an Anonymous (1970) study for which only an abstract was available. However, some limited study details were available. DBA was administered in three drops to the rabbit eye (no vehicle), and were observed for “a few days” without washing. The exposure induced “only very slight changes in the conjunctivae, which were fully reversible within a few days.”

DBA, skin sensitization

Anonymous (1989, as cited by ECHA, 2018c) conducted an OECD Guideline 406 guinea pig maximization test with DBA. In the induction period, 20 female Albino guinea pigs were

³ Referred to as its German name, adipinsäure-di-n-butylester

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% sodium dodecyl sulfate (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.

In a separate maximization test (Cognis Deutschland GmbH and Co., 2002, as cited by Andersen, 2006; also reported as Anonymous, 1972 by ECHA, 2018c), five male Pirbright-White-W58 guinea pigs were injected intradermally (10 times at 2-day intervals) with 0.1 mL of 25% DBA (unspecified vehicle). The guinea pigs were challenged 14 days later (location not reported) with an unspecified dose of DBA. There was slight reddening at the injection site that subsided within 2 days, but no evidence of dermal sensitization.

DiBA, skin irritation

In a study described as similar to an OECD Guideline 404 study, the shaved (*sic*) skin of an unspecified number of volunteers was treated with an unnamed chemical (assumed to be DiBA, 100%) for 24 hours. There was no indication of irritation during the 48-hour observation period (Anonymous, 1969, as cited by ECHA, 2018d). In another human study reported as comparable to OECD Guideline 404 (Anonymous, 1967, as cited by ECHA, 2018d), 20 volunteers were treated with 100% of an unnamed chemical (assumed to be DiBA) on shaved (*sic*) skin for 20 days. The coverage was described as open, but also identified the use of a "test plaster." There was no indication of irritation during the 34-day evaluation period (with the first observation at 12 hours). No systemic toxicity endpoints were evaluated.

In a study reported to be similar to an OECD Guideline 404 study, mice (strain unspecified) were exposed twice a day for 14 days (occlusion not specified) to an undiluted unnamed chemical (assumed to be DiBA, volume not specified) (Anonymous, 1969, as cited by ECHA, 2018d). The animals were observed for what appears to be an additional 14 days. No other study details were provided, and the study conclusion was no "indication of irritation." Apparently the same report (Anonymous, 1969, as cited by ECHA, 2018d) reported a second experiment similar to OECD Guideline 404, in which rabbits (number, strain unspecified) were treated with an undiluted unnamed chemical (assumed to be DiBA). In this study, the chemical was applied to shaved skin (occlusion not specified) for 1 day with 1 day of observation. No other study details (including volume applied) were provided. The authors concluded that there was no indication of irritation.

DiBA, eye irritation

Anonymous (1969, as cited by ECHA, 2018d) also conducted an eye irritation test comparable to OECD Guideline 405. There was no indication of irritation when an unnamed chemical (presumably DiBA) was instilled into a rabbit eye. No other details were available, although the study was considered reliable with restrictions.

DiBA, sensitization

ECHA (2018d) reported on a study comparable to OECD Guideline 406 Draize test conducted on 20 male and female volunteers exposed to an unnamed chemical (assumed to be DiBA). No other study details (including any information on the nature of the challenge) were provided. There was no indication of sensitization at 12 hours after the “rechallenge.”⁴ (Anonymous, 1967, as cited by ECHA, 2018d).

5.2 Repeated Dose Toxicity

DBA

In a Good Laboratory Practices (GLP)-compliant study conducted according to OECD Guideline 407, 5-week old Crj: CD(SD) rats (6/sex/dose) were exposed by oral gavage in olive oil to 0, 20, 140, or 1000 mg/kg-day DBA by gavage in olive oil for 28 days. Additional satellite groups of 6/sex/dose (control and high dose) were sacrificed after a 14-day recovery period. Endpoints evaluated included hematology, clinical chemistry, urinalysis and histopathology, but did not include neurological evaluations. No adverse treatment-related effects were reported, and the high dose of 1000 mg/kg-day was a NOAEL (MHW, 1996b, as cited by OECD, 1996, ECHA, 2018c).

No high-quality repeated dose studies with DBA are available via the inhalation route. In a poorly-documented study, rats and mice were exposed to DBA continuously via inhalation (24 hours/day, 7 days/week), for 4 months at concentrations of 0.044, 0.45, or 5.0 mg/m³ (Astapova et al., 1990, as cited by ECHA, 2018c). It is not clear whether there was a clean air control. For the rat study, ECHA (2018c) listed an effect level of 0.45 mg/m³, based on unspecified critical effects, while an effect level of 0.45 mg/m³-day was listed for the mouse study, based on “change in reflex activity, barrier change of neuromuscular stimulation.” No other study details were available, and ECHA (2018c) disregarded both studies due to the limited reporting. The information is insufficient to identify a NOAEL or LOAEL for either study, and the studies are of insufficient quality to include in Table 3.

Andersen (2006) summarized two repeated-dose dermal studies of DBA conducted by the Mellon Institute of Industrial Research (1950). In the first study, 10 rabbits/dose were administered DBA⁵ topically five times per week for 6 weeks at doses of 0 (untreated control), 0.5 or 1.0 mL/kg-day in 20% Tergitol 7. Based on a density of 0.962 g/mL, the doses were equivalent to 481 and 962 mg/kg-day, 5 days/week (daily average of 343 and 687 mg/kg-day). Deaths were reported for five high-dose rabbits and one rabbit at the low dose, but the deaths were reported as being unrelated to treatment. No further information was provided on the reason for the death. Decreased body weight gain was reported at both doses, but was significant only at the high dose. Gross necropsy found slight cloudy swelling of the renal convoluted and loop

⁴ It was not clear whether this “rechallenge was truly a second challenge,” or whether this was the challenge dose, and the “1st reading” was really the initial induction phase, even though the results were listed as “no sensitization.”

⁵ Andersen (2006) noted that the report listed the test compound as n-butyl adipate, while it should have been listed as di-n-butyl adipate).

tubules in one low-dose rabbit and one high-dose rabbit. One high-dose rabbit also had slight cloudy hepatic swelling. Based on these results, ECHA (2018c) considered the low dose to be a LOAEL. However, the study is limited by the high death rate from some undetermined cause, and the lack of detailed study information. In addition, the endpoint evaluation was much more limited than modern methods, lacking endpoints such as histopathology, clinical chemistry and hematology analysis. ECHA (2018c) labeled the study “disregarded” in light of these deficiencies.

In the second study by the Mellon Institute of Industrial Research (1950), 4 dogs/sex/dose were “soaked” twice a week with an emulsion of 6.25% DBA in water (with 0.625% Emulsifier 75 H 14S) for 14 weeks (Andersen, 2006). The control group (2 dogs) were treated only with the vehicle emulsifier. The “retained dose” was estimated to be 1 mL/kg. It appears that the only systemic effect evaluated was body weight, for which no significant effect was observed. Slight desquamation but no erythema was observed on the skin of three treated dogs and one control. ECHA (2018c) listed the study as “disregarded,” but identified the single tested dose as a NOAEL 125 mg/kg-day; this NOAEL is not reliable, due to the limited range of endpoints evaluated. No further details are available.

RTECS (2018) cited a 1996 article reporting the lowest toxic dose in a dermal repeated dose study as 30 mL/kg for 6 weeks in rabbits. The reported effects were “nutritional and gross metabolic effects” including weight loss or decreased weight gain. No other study details were provided.

DiBA

ECHA (2018d) reported on a GLP-compliant repeat-dose study conducted under OECD Guideline 407 for an unnamed chemical (assumed to be DiBA). In this study, groups of male and female Sprague Dawley rats⁶ were exposed to 0, 20, 140, or 1000 mg/kg-day DiBA by oral gavage (vehicle unspecified) once daily for 28 days (ECHA, 2018d). A wide variety of endpoints was evaluated, including body weight, hematology, clinical chemistry, hematology, and histopathology, with no treatment-related adverse effects. The high dose of 1000 mg/kg-day is a NOAEL in this study (MHW, 1996⁷, as cited by ECHA, 2018d).

Note that it is not clear if the oral repeat-dose study listed for DiBA is the same as that listed for DBA, or if these are in fact different studies. ECHA cited both studies as “unnamed report” from 1996. Although the DBA dossier specifically identifies DBA as the test chemical, the DiBA dossier lists an unnamed chemical. However, because other entries for DiBA were listed as “unnamed chemical” where the study was included only in the DiBA dossier (and not the DBA dossier), and because the study listed under DiBA is described as a “key study,” rather than “read-across,” it is reasonable to assume that the study is indeed for DiBA.

⁶ Number per sex/dose not reported, but presumably at least 5/sex/dose, since the study was described as being fully guideline compliant.

⁷ It is not clear whether this study corresponds to the studies listed in the reference list as MHW 1996a, MHW 1996b, or is a third study, and so no letter is included in the citation.

No repeat-dose inhalation or dermal studies were identified for DiBA.

5.3 Chronic Toxicity/Carcinogenicity

No chronic studies were identified for DBA or DiBA.

5.4 Reproductive Toxicity

DBA

MHW (1996a, as cited by OECD, 1996, ECHA, 2018c) conducted a reproductive/developmental toxicity screening test with DBA according to OECD Guideline 421. In this study, 8-week old male and female Sprague Dawley rats (13/sex/dose) were treated with DBA in corn oil by oral gavage at 0, 100, 300, or 1000 mg/kg-day, starting at 14 days prior to mating. Males were exposed for a total of 42 days and females until day 3 of lactation, after which the parental animals and F1 offspring were sacrificed. Increased salivation was reported at a dose-related incidence, but was considered to reflect test article stimulation, rather than being a neurological effect. Mean body weight was slightly decreased in high-dose parental males, but the decrease was not statistically significant; no quantitative data were provided. Relative kidney weight was increased in the highest dose group (statistically significant in males, $p < 0.05$). Relative spleen weight in males was significantly increased at 100 and 1000 mg/kg-day and absolute spleen weight was significantly increased in females at 100 mg/kg-day, but the changes were not dose-related and were likely a result of random variability. There were no other systemic effects on the parental animals, and no effects on reproductive indices, histopathology of reproductive organs, sperm measures, or estrous cycle. The increase in relative kidney weight was only 8%, but it was dose-related, suggesting a minimal LOAEL of 1000 mg/kg-day in males for effects on the kidney; the effect on relative kidney weight in females was not statistically significant and $< 10\%$, and so it was not considered adverse for this assessment⁸. The reproductive NOAEL was 1000 mg/kg-day, the highest dose tested. In the F1 generation, pup viability on postnatal day (PND) 4 was significantly ($p < 0.05$) decreased (by about 10%) at the 1000 mg/kg-day dose, but there was no significant effect on pup weight or on gross necropsy, although there was a slight nonsignificant decrease in pup weight. Therefore, the developmental NOAEL was 300 mg/kg-day, based on decreased pup viability. This study was only a screening study, included fewer animals than are tested in a full reproductive or developmental study, and did not expose the males for their entire period of spermatogenesis.

DiBA

MHW (1996, as cited by ECHA, 2018d) conducted a GLP-compliant reproductive/developmental toxicity screening test with an unnamed chemical (assumed to be DiBA) according to OECD Guideline 421. Male and female Sprague Dawley rats were exposed to DiBA at 0, 100, 300, or 1000 mg/kg-day by oral gavage in corn oil starting at 14 days prior to mating. Males were exposed for a total of 42 days and females until day 3 of lactation. A slight

⁸ ECHA (2018) and OECD (1996) listed 300 mg/kg-day as a NOAEL for both males and females, based on the increased kidney weight.

decrease in body weight was reported in high-dose males, but was not considered treatment-related. Increased kidney weight was reported in males and females at the high dose, but it was unclear whether the increase was in relative or absolute weight, and no further details were provided. No other effects, including no effects on reproductive indices, sperm measures, or estrous cycle, were reported. Therefore, the NOAEL for kidney effects was reported as 300 mg/kg-day in males and females, based on increased kidney weight⁹. The reproductive NOAEL was 1000 mg/kg-day, the highest dose tested. In the F1 generation, there were slight decreases in pup weight on PND 0 and 4 and decreased pup viability on PND 4 at the 1000 mg/kg dose; no other effects were reported. Therefore, the developmental NOAEL was 300 mg/kg-day in the F1 generation for pup viability. As for the similar study conducted with DBA, this study was only a screening study, included fewer animals than are tested in a full reproductive or developmental study, and did not expose the males for their entire period of spermatogenesis.

An additional issue is that it is not clear if the reproductive screening study listed for DiBA is the same as that listed for DBA, or if these are in fact different studies. Although the essentially identical findings could simply reflect the similarity of the two chemicals, the details listed for DiBA are much less extensive than those provided for DBA. In particular, the primary numerical data are provided for DBA (including means and standard deviations for kidney weight and pup viability), allowing for an independent evaluation of the data, while only text summaries and fewer experimental details are provided for DiBA. This also means that it is not possible to determine whether the two studies were separate studies with similar results, or duplicate reporting of the same study. It is also puzzling why the dossier for DBA names the chemical, while the DiBA dossier lists an unnamed test material. However, the result for DiBA is listed as a “key study,” not “read across,” and ECHA read-across entries usually list the chemical being used as a surrogate.

5.5 Prenatal, Perinatal, and Postnatal Toxicity

Aside from the results from the screening studies described in Section 4.4, no data were identified regarding the developmental toxicity of DBA or DiBA via the oral, inhalation or dermal routes.

5.6 Genotoxicity

DBA

In an Ames bacterial reverse mutation assay, DBP was tested in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 with and without exogenous metabolic activation (Henkel KgaA, 1996, as cited by Andersen, 2006, with detailed information in ECHA, 2018c). Two studies were conducted, one up to 5000 µg/plate, and the other up to 1000 µg/plate, with cytotoxicity observed at concentrations ≥ 250 µg/plate. In another Ames bacterial reverse mutation assay, DBA was tested in *S. typhimurium* strains TA 1535, TA 1537, TA 98, TA 100, and *Escherichia coli* WP2 *uvrA* with and without S9 activation, in two tests up to 5000 µg/plate

⁹ The ECHA (2018d) summary listed clinical signs as the basis for the parental systemic NOAEL, but no clinical signs are noted anywhere else in the entry, so this appears to be an error.

(Anonymous, 1996, as cited by ECHA, 2018c). All strains were negative in both tests. A third Ames assay was conducted by Hachiya and Takizawa (1994, as cited by CCRIS, 2018). This study was conducted in *S. typhimurium* strains TA 97, TA 98, TA 100, TA 102, and *E. coli* WP2 pKM101 +/-S9, up to 10,000 µg/plate, and was negative under all test conditions. OECD (1996) also reported negative results in *S. typhimurium* strains TA 100, TA 1535, TA 98, TA 1537 and *E. coli* WP2 *uvrA* using the preincubation method at concentrations up to 5000 µg/plate +/-S9 (MHW, 1996b, as cited by OECD, 1996)¹⁰.

In an *in vitro* mammalian chromosome aberration test, DBA was tested in Chinese hamster lung (CHL/IU) cells with and without metabolic activation (MHW, 1996b, as cited by OECD, 1996, ECHA, 2018c). Treatments without S9 were 6 hours (0.012, 0.023, 0.046 mg/mL), 24 hours (0.7, 1.3, 2.6 mg/mL), and 48 hours (0.7, 1.3, 2.6 mg/mL). Treatments with S9 were for 6 hours (0.7, 1.3, 2.6 mg/mL). The high dose was approximately the limit dose of 10 mM, and did not cause cytotoxicity (OECD, 1996). DBA was positive for chromosome aberrations with metabolic activation at 0.7 mg/mL, but negative without metabolic activation at all doses.

An *in vivo* mammalian erythrocyte micronucleus test was conducted in NMRI mice (RCC Cytotest Cell Research GmbH, 2002, as cited by Andersen, 2006, with additional details reported by ECHA, 2018c). The high dose of 2000 mg/kg was chosen based on the results of a range-finding study, in which no signs of toxicity were seen in two male and two female NMRI mice treated with the limit dose of 2000 mg/kg. In the definitive study, six NMRI mice/sex/dose¹¹ were treated with DBA *via* oral gavage in olive oil at doses up to 2000 mg/kg. Bone marrow from treated animals was collected at 24 hours and 48 hours after DBA administration for micronucleus analysis. DBA was negative for micronucleus formation at all doses.

The positive controls behaved as expected in all of the genotoxicity studies.

DiBA

Hachiya and Takizawa (1994, as cited by CCRIS, 2018) tested DiBA in the Ames assay in *S. typhimurium* strains TA 97, TA 98, TA 100, TA 102, and *E. coli* WP2 with and without exogenous metabolic activation, at concentrations up to 10,000 µg/plate, and found no evidence of mutagenicity. In another bacterial reverse mutation assay, an unnamed chemical (assumed to be DiBA) was tested up to 5000 µg/plate with or without S9 activation using *S. typhimurium* strains TA 1535, TA 1537, TA 98, TA 100, and *E. coli* WP2, and was negative in all strains (Anonymous, 1996, as cited by ECHA, 2018d). It appears likely that the Ames study for DiBA was actually conducted with DBA. Not only did both studies refer to the same reference and use the same protocol, but the executive summary for genetic toxicity refers to “Dibutyl adipate”, rather than DiBA. It is puzzling, however, why ECHA (2018d) listed the study as a key study, rather than as “read-across.”

In an *in vitro* mammalian chromosome aberration test, an unnamed chemical (assumed to be DiBA) was tested in Chinese hamster lung (CHL/IU) cells with and without metabolic activation

¹⁰ This may be the same study as cited by ECHA (2018c), but ECHA did not mention the use of the preincubation method.

¹¹ ECHA (2018c) noted that 6/sex/dose were treated, but only 5/sex/dose were evaluated.

(MHW, 1996, as cited by ECHA, 2018d). Treatments without S9 included “continuous treatment” (unspecified duration) with 0, 0.7, 1.3, 2.6 mg/mL, or “short-term” treatment with 0, 0.012, 0.023, 0.046 mg/mL. Treatments with S9 included short-term treatment with 0, 0.7, 1.3, 2.6 mg/mL. The high dose was approximately the limit dose of 10 mM, and there was no cytotoxicity. The test material was negative in the absence of S9. ECHA (2018d) reported in one part of the summary that the test material was negative with S9, but in another part reported that structural chromosome aberrations were observed with metabolic activation. As for the Ames assay, it is not clear whether the test material was DBA or DiBA.

The positive controls behaved as expected in the genotoxicity studies.

5.7 Mechanistic Studies

DBA

In vitro cytotoxicity to HeLa cells was investigated following either 24-hour metabolic inhibition test (MIT) or a 7-day incubation for viability (Ekwall et al., 1982). DBA showed minimal inhibitory concentrations for partial inhibition of 140 mg/mL after 24 hours and after 7-days exposure, leading the authors to conclude DBA is not acutely toxic based on low solubility. The 7-day IC₅₀ was 8.7 g/L (Ekwall et al., 1982).

DiBA

No data.

5.8 Mode of Action

In light of the very low toxicity seen with DBA and DiBA and the few reported nonspecific adverse effects, no MOA evaluation is possible. The weight of the evidence is that DBA and DiBA do not cause gene mutations (Henkel KgaA, 1996, as cited by Andersen, 2006, with detailed information in ECHA, 2018c; Anonymous, 1996, as cited by ECHA, 2018c and 2018d; MHW, 1996b, as cited by OECD, 1996; Hachiya and Takizawa, 1994, as cited by CCRIS, 2018a, 2018b). However, no mammalian cell gene mutation assays are available for either chemical. Both chemicals caused structural chromosome damage in CHL cells in the presence of metabolic activation (MHW, 1996b, as cited by OECD, 1996, ECHA, 2018c; MHW, 1996, as cited by ECHA, 2018d) (recognizing that the reporting for DiBA included positive and negative statements). However, DBA was negative for chromosome damage in the micronucleus assay *in vivo* (RCC Cytotest Cell Research GmbH, 2002, as cited by Andersen, 2006, with additional details reported by ECHA, 2018c), indicating that overall DBA should not be considered clastogenic.

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

Although a number of repeated-dose studies are available for DBA and (apparently) DiBA, most of them were conducted prior to modern testing methods and/or were inadequately documented, so only limited reliable data are available. There was no evidence of systemic toxicity in a well-

conducted study of rats exposed to DBA by gavage for 28 days to doses up to 1000 mg/kg-day (MHW, 1996b, as cited by OECD, 1996, ECHA, 2018c). Similarly, there was no systemic toxicity in a well-conducted study of rats treated with a compound assumed to be DiBA by gavage for 28 days at doses up to 1000 mg/kg-day (MHW, 1996, as cited by ECHA, 2018d). However, it is unclear whether this latter report was truly a study on DiBA, or whether it was read-across from DBA.

The only systemic target reported in the available studies was the kidney. Increased relative kidney weight was reported in a screening reproductive/developmental toxicity study in male and female rats gavaged with 1000 mg/kg-day DBA (MHW, 1996a, as cited by OECD, 1996, ECHA, 2018c), although there is some uncertainty regarding the degree of adversity, as discussed in the next section. There is some suggestion that the kidney may have also been a target via the dermal route of exposure. In a dermal study with rabbits treated topically with doses calculated to be to 481 and 962 mg/kg-day, 5 days/week for 6 weeks (daily average of 343 and 687 mg/kg-day), gross necropsy reported renal lesions (Mellon Institute of Industrial Research, 1950, as cited by Andersen, 2006). However, this study cannot support the determination of an effect level, because it was conducted prior to modern toxicology testing methods, documentation is limited, there was no dose-response, and the study lacked a histopathology evaluation.

Similarly to DBA, the kidney was the only systemic target identified for DiBA, although primary data were not available, making it even harder to evaluate adversity. Increased relative kidney weight was reported in a screening reproductive/developmental toxicity study in male and female rats gavaged with 1000 mg/kg-day DiBA (MHW, 1996, as cited by ECHA, 2018d), although there is some uncertainty as to whether the test material was DiBA or DBA.

It is of interest that, for both chemicals, a dose of 1000 mg/kg-day caused increased kidney weight in the reproductive/developmental screening study, but not the 28-day systemic toxicity study. This likely reflects the difference in study duration, with the former study involving exposure for 42 days, since both studies were done with Sprague Dawley rats.

There were no reproductive effects in a screening study with male and female rats treated by gavage at doses up to 1000 mg/kg-day DBA (MHW, 1996a, as cited by OECD, 1996, ECHA, 2018c) or a chemical assumed to be DiBA (MHW, 1996, as cited by ECHA, 2018d). As for systemic toxicity, it is unclear whether the latter study evaluated DiBA or DBA.

Developmental toxicity data for both chemicals are limited to the pup data from the reproductive/developmental toxicity screening study (MHW, 1996a, as cited by OECD, 1996, ECHA, 2018c; MHW, 1996, as cited by ECHA, 2018d). Decreased pup viability was reported on PND 4 in the offspring of dams treated with 1000 mg/kg-day of either DBA or the chemical assumed to be DiBA. At this dose, there was also a slight nonsignificant decrease in pup weight on PND 4 with DBA, and on PND 0 and 4 with the chemical assumed to be DiBA.

No data are available regarding the carcinogenic potential of DBA or DiBA.

DBA and (presumably) DiBA were negative for gene mutation in well-conducted bacterial reverse mutation assays (Henkel KgaA, 1996, as cited by Andersen, 2006, with detailed information in ECHA, 2018c; Anonymous, 1996, as cited by ECHA, 2018c and 2018d; MHW, 1996b, as cited by OECD, 1996; Hachiya and Takizawa, 1994, as cited by CCRIS, 2018a, 2018b). Chromosome aberrations were observed with both chemicals in CHL cells (apparently for DiBA, given the inconsistency in the dossier) (MHW, 1996b, as cited by OECD, 1996, ECHA, 2018c; MHW, 1996, as cited by ECHA, 2018d). However, DBA was not clastogenic in the micronucleus assay in vivo (RCC Cytotest Cell Research GmbH, 2002, as cited by Andersen, 2006, with additional details reported by ECHA, 2018c).

5.10 Uncertainties and Data Gaps

Database:

There are a number of data gaps for DBA, and the gaps for DiBA are even larger. A good-quality 28-day repeated-dose toxicity study is available for DBA via the oral route (MHW, 1996b, as cited by ECHA, 2018c, Andersen, 2006), but there are no high-quality repeated-dose studies via the inhalation or dermal routes, and no high-quality systemic toxicity studies longer than 28 days. A good quality reproductive/developmental screening study via the oral route is available for DBA (MHW, 1996a, as cited by ECHA, 2018, OECD, 1996), but it is only a screening study, and no definitive study is available for reproductive or developmental toxicity. Chronic/carcinogenicity data and a gene mutation study in mammalian cells are also missing.

The high-quality data for DiBA appear to be almost the same as that for DBA, with the same issues on data gaps applying. The high-quality data consist of a 28-day repeated dose oral toxicity study, a screening oral reproductive/developmental study, and genetic toxicity studies. No definitive study is available for reproductive or developmental toxicity. Chronic/carcinogenicity data, as well as a gene mutation study in mammalian cells and *in vivo* cytogenicity data are also missing. Unlike the situation for DBA, only text summaries are available for DiBA; none of the primary data are available. In addition, the ECHA (2018d) dossier lists the test chemical as “unnamed” in the DiBA dossier. Due to the near-identity of the study design and test results for DBA and DiBA, it is not clear based on the text alone whether the studies were really with DiBA, or whether the DBA results are shown. Data on acute dermal and inhalation toxicity are also lacking for DiBA.

Hazard

Acute toxicity: Inconsistencies between the reporting in secondary sources and the absence of access to primary data make it hard to evaluate the acute oral toxicity of DBA. Although most of the reported LD₅₀ values were very high (>10,000 mg/kg), OECD (1996) cited one secondary source (Frear, 1976) as having an LD₅₀ <2000 mg/kg. A more modern study also reported an LD₅₀ <2000 mg/kg. A similar situation exists for DiBA, with most studies reporting a high LD₅₀ >10,000 mg/kg, but one more recent study reporting an LD₅₀ of 1290 mg/kg (Anonymous, 1996, as cited by ECHA, 2018d). This report for DiBA may actually be a DBA study, and it is not clear if the lower LD₅₀ reflects a typographical error.

Kidney: Increased kidney weight was seen in male and female rats treated with DBA or DiBA. The degree of adversity in the DiBA study cannot be determined, in the absence of the numerical data.

Liver: No effects were seen on the liver in any study with DBA or DiBA, except for liver congestion in an acute oral study and slight cloudy hepatic swelling in a 6-week dermal study. Both of these studies were conducted prior to modern test methods. In contrast, DEHA, which ECHA used as a surrogate in read-across evaluations for DBA, is a known peroxisome proliferator, causing increased liver weight. No evidence of peroxisome proliferation was seen with DBA or DiBA, but the LOAEL for peroxisome proliferation for DEHA was above the highest dose tested for DBA or DeBA in high-quality repeated-dose studies.

Neurological: There is some suggestion of neurological effects in an inhalation study with DBA (Astapova et al., 1990, as cited by ECHA, 2018c), but the study reporting these effects was poorly reported and does not appear to have been conducted using modern methods. No clinical signs indicating neurological effects of DBA or DiBA have been reported, but no systematic evaluation of neurotoxicology using standard methods has been conducted.

Reproductive toxicity: No effects were seen in the guideline-compliant screening study, but the conclusions are limited by the limitations of the screening study, including relatively small sample sizes and exposure of males for only a portion of the spermatogenic cycle.

Developmental toxicity: No uncertainties regarding the available data for developmental toxicity were identified, recognizing that no standard developmental toxicity study has been conducted and no histopathological evaluation of pups was conducted in the screening study.

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

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified ¹	Toxicological Basis	Comments
Oral					
Crj: CD(SD) rat (M and F) (6/sex/dose; additional 6/sex/dose for control and high-dose satellite) MHW, 1996b, as cited by ECHA, 2018c, Andersen, 2006	28 days Oral gavage in olive oil 0, 20, 140, or 1000 mg/kg-day	Systemic toxicology	NOAEL = 1000	No adverse effects observed	Compliant to GLP and OECD Guideline 407, except that neurological evaluations were not conducted
Sprague Dawley rat (M and F) (13/sex/dose) MHW, 1996a, as	M and F beginning 14 days prior to mating M total of 42 days	Kidney	NOAEL = 300 (M) Minimal LOAEL = 1000 (M) NOAEL = 1000 (F)	Increased relative kidney weight	Compliant to GLP and OECD Guideline 421 Increase in males was statistically significant and dose-related but <10% Effect in females not statistically significant and <10%, so not considered to be adverse.

¹ 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 ¹	Toxicological Basis	Comments
cited by ECHA, 2018c, OECD, 1996	F through day 3 of lactation				ECHA (2018) and OECD (2006) considered 1000 mg/kg-day to be a systemic LOAEL for both sexes
	Oral gavage in corn oil 0, 100, 300, or 1000 mg/kg-day	Reproductive	NOAEL = 1000 (M, F)	No effect	This study was only a screening study, included fewer animals than are tested in a full reproductive or developmental study, and did not expose the males for their entire period of spermatogenesis.
		Developmental	NOAEL = 300 LOAEL = 1000	Decreased pup viability on PND 4	

Table 4. Summary of NOAELs/LOAELs Identified for DiBA by Organ System

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day) unless otherwise specified ²	Toxicological Basis	Comments
Oral					
Sprague-Dawley rat (M and F) Number/sex/dose not reported	28 days Oral gavage (vehicle not specified)	Systemic toxicology	NOAEL = 1000	No adverse effects observed	It is not clear if the repeat-dose study listed for DiBA is the same as that listed for DBA, but they appear to be different studies, since the entry was not identified as read-across.

² 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 ²	Toxicological Basis	Comments
MHW, 1996, as cited by ECHA, 2018d	0, 20, 140, or 1000 mg/kg-day				
Sprague Dawley rats (M and F) (13/sex/dose) MHW 1996, as cited by ECHA, 2018d	M and F beginning 14 days prior to mating M total of 42 days F through day 3 of lactation Oral gavage (vehicle not specified) 0, 100, 300, or 1000 mg/kg-day	Systemic toxicology	NOAEL = 300 (M, F) LOAEL = 1000 (M, F)	Increased kidney weight	Compliant to GLP and OECD Guideline 421 This study was only a screening study, included fewer animals than are tested in a full reproductive or developmental study, and did not expose the males for their entire period of spermatogenesis. The tested chemical was “unnamed,” but presumed to be DiBA. Due to the similar results and identical citation, it is unclear whether this was truly a study with DiBA, or read-across from DBA. Unlike for the similar DBA study, quantitative results were not reported, and so it was not possible to determine whether the results were similar but for different chemicals.
		Reproductive	NOAEL = 1000 (M, F)	No effect	
		Developmental	NOAEL = 300 LOAEL = 1000	Decreased pup viability on PND 4	

6 Exposure

The use of DBA and DiBA in consumer products has been described in Section 3 of this report. The general population may be exposed to DBA or DiBA through dermal contact with toys and consumer products (including cosmetics); via inhalation from personal care products (e.g., hair sprays); 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; through contaminated drinking water; and, by inhalation and ingestion of contaminated household dust.

DBA

Very little information is available on the amount of DBA exposure from consumer uses. DBA is used in consumer floor wax and OECD (1996) estimated a dose of 3.6 mg/kg for one housekeeping event using floor wax.

Wei et al. (2009) measured migration of DBA from polyvinylidene chloride (PVDC) packaging film (containing 25 µg/g DBA) into ham sausage to demonstrate and validate a GC/MS method and to determine adipate plasticizer migration from PVDC packaging film. Migration decreased progressively with depth from the surface to the center of the sausage and concentration increased with time. Within four months, approximately 6.7% of the DBA in the film migrated into the sausage and DBA reached the innermost part of the sausage within six months.

OECD (1996) discussed potential human exposure situations. For the public, the highest potential exposure would be expected to be from drinking water (from surface water) (assumed concentration less than 0.004 mg/L) (OECD, 1996). OECD noted that DBA is not expected to be significantly removed during drinking water processing, due to its physical-chemical properties.

OECD (1996) reported that DBA is produced in a closed system, but worker exposure may occur when the product is filled into barrels. Dermal exposure would be the main exposure route with inhalation less of a concern because DBA vapor pressure is low (OECD, 1996).

Guo et al. (2010) tested serum from 10 female volunteers with no occupational exposure to plasticizers to demonstrate a gas chromatography-mass spectrometry assay. The mean concentration of DBA was 9.4 (+/- 5.2) ng/mL (range ND - 13.5 ng/mL).

DiBA

Several investigators have detected or measured DiBA in toys and childcare articles. A 2007 survey in the Netherlands of soft plastic toys (n= 200) and childcare articles (n=12) found DiBA in 0.6 percent of sampled items (FCPSA 2008, as cited by Maag et al., 2010). Abe et al. (2012) measured plasticizers in 101 samples of PVC toys on the Japanese market. They found DiBA in

2% of the “designated toys”¹ samples (mean concentration [detected samples only] of 0.76%) and in none of the “not-designated” toys samples.

Subedi et al. (2017) collected 28 indoor dust samples (eleven childcare facilities, three salons, and eleven homes) in the U.S. during 2016, using vacuum cleaners (no further details regarding collection or equipment was provided). DiBA concentrations in the dust ranged from not detected in six location samples to 56.4 µg/g (measured in a salon). This concentration was toward the middle of the range of concentrations measured for several non-phthalate plasticizers (range 0.51 to 880 µg/g). The authors calculated daily intake (from dust ingestion and dermal uptake) from indoor dust for various age groups in the three environments. The highest intake levels estimated for DiBA from dust ingestion and dermal uptake were for infants in the home (5.43 ng/kg-day and 0.0300 ng/kg-day, respectively).

The FDA has listed DiBA as an indirect food additive to be used only as a component of adhesives (HSDB, 2018). JECFA (2011) listed DiBA as a flavoring agent, with a highest estimated daily intake (SPET, single portion exposure technique) of 1000 µg/day (17 µg/kg-day), and concluded that there are no safety concerns at current levels of intake when used as a flavoring agent. JECFA also reported that DiBA occurs naturally in food, but did not provide any quantitative data.

Guo et al. (2010) tested serum from 10 female volunteers with no occupational exposure to plasticizers to demonstrate a gas chromatography-mass spectrometry assay. DiBA was not detected in any of the samples.

7 Discussion

7.1 Toxicity Under FHSA

Animal data were sufficient to support the conclusion that **DBA does not fit the designation of acutely toxic under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A))** following dermal exposure, based on a dermal LD₅₀ of about 19,000 mg/kg (Smyth et al., 1951). However, the data are **insufficient to determine whether DBA or DiBA fit the designation of acutely toxic under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A))** following single oral or inhalation exposures, or whether DiBA fits the designation following single dermal exposure. Although most of the oral data support oral LD₅₀ values >10,000 mg/kg for both chemicals, some studies have reported LD₅₀

¹ Japanese publication with abstract and tables only in English. We assumed “designated” refers to those toy types that are defined as “designated toys” in Article 78 of the Ordinance for Enforcement of the Food Sanitation Act (revised in March 2008) (<https://www.jetro.go.jp/en/reports/regulations/pdf/foodext201112e.pdf>). “Designated toys” include those toys intended to come into direct contact with an infant’s mouth, infant jewelry, decal sticker toys, roly-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.

values of 1290-1520 mg/kg for DBA (Frear, 1976, as cited by OECD, 1996, but not as cited by RTECS, 2018; Cognis Deutschland GmbH & Co, 2002, as cited by Andersen, 2006) and of 1290 mg/kg for DiBA (Anonymous, 1996, as cited by ECHA, 2018d); the reason for the discrepancy is not known. The inhalation data for DBA are insufficient for identifying an LC₅₀, and no acute dermal or inhalation data are available for DiBA.

DBA was slightly irritating to the skin of humans (Cognis Deutschland GmbH and Co., 2002, as cited by Andersen, 2006) and rabbits (Anonymous, 1989, as cited by ECHA, 2018c), although moderate skin irritation was observed with rabbits treated for prolonged periods in early studies (Mellon Institute of Industrial Research, 1951, as cited by Andersen et al., 2006).

DBA was not irritating to the eye of humans (Cognis Deutschland GmbH and Co., 2002, as cited by Andersen, 2006) or rabbits in a guideline study (Anonymous, 1989, as cited by ECHA, 2018c), although another study reported slight irritation in rabbits (Cognis Deutschland GmbH & Co., 2002, as cited by Andersen, 2006). DBA was not a sensitizer in the guinea pig maximization test (Anonymous, 1989, as cited by ECHA, 2018c; Cognis Deutschland GmbH and Co., 2002, as cited by Andersen, 2006; also reported as Anonymous, 1972 by ECHA, 2018c).

DiBA was not irritating to the skin of humans, mice, or rabbits, or to the rabbit eye (Anonymous, 1969, 1967, both as cited by ECHA, 2018d). There was no evidence of sensitization in a human test, but the results were poorly documented (Anonymous, 1967, as cited by ECHA, 2018d).

Systemic toxicity of both DBA and DiBA is low, with effects limited to the kidney after exposure to 1000 mg/kg-day for 42 days (MHW, 1996a, 1996b, as cited by ECHA, 2018c; MHW, 1996, as cited by ECHA, 2018d).

No evidence of reproductive toxicity was seen in reproductive/developmental screening assays that tested DBA and DiBA up to 1000 mg/kg-day (MHW, 1996a, as cited by ECHA, 2018c; MHW, 1996, as cited by ECHA, 2018d). These studies also found a small but statistically significant decrease in pup viability at the high dose, but no other developmental effects.

The weight of the evidence is that DBA and DiBA do not cause gene mutations (Henkel KgaA, 1996, as cited by Andersen, 2006 and ECHA, 2018c; Anonymous, 1996, as cited by ECHA, 2018c and 2018d; MHW, 1996b, as cited by OECD, 1996; Hachiya and Takizawa, 1994, as cited by CCRIS, 2018a, 2018b). It appears that both chemicals caused structural chromosome damage *in vitro* in the presence of metabolic activation but not in its absence (MHW, 1996b, as cited by OECD, 1996, ECHA, 2018c; MHW, 1996, as cited by ECHA, 2018d). However, DBA was negative for chromosome damage in the micronucleus assay *in vivo* (RCC Cytotest Cell Research GmbH, 2002, as cited by Andersen, 2006 and ECHA, 2018c), indicating that overall DBA should not be considered clastogenic.

No data are available on the carcinogenic potential of DBA or DiBA.

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² Report date is listed as 1990, even though the study year is listed as 1970.

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APPENDIX 1

Search Terms Used

Toxline, DBA: (Di-butyl adipate) OR (Di-n-butyl adipate) OR (Dibutyl adipate) OR (dibutyl ester hexanedioic acid) OR (Butyl adipate) OR (Dibutyl hexanedioate) OR (dibutyl ester adipic acid) OR (1,6-dibutyl ester hexanedioic acid) OR (dibutyl ester hexanedioic acid) OR (141-04-8)

Toxline, DiBA: "diisobutyl adipate" OR "Bis(2-methylpropyl) hexanedioate" OR "Diisobutyl hexanedioate" OR "diisobutyl ester hexanedioic acid" OR "bis(2-methylpropyl) ester hexanedioic acid" OR "Adipic acid bis(2-methylpropyl) ester" OR "1,6-bis(2-methylpropyl) ester hexanedioic acid" OR "diisobutyl ester adipic acid" OR "Plasthall DIBA" OR "DiBA" OR (105-99-7)

Pubmed, DBA: (Di-butyl adipate) OR (Di-n-butyl adipate) OR (Dibutyl adipate) OR (dibutyl ester hexanedioic acid) OR (Butyl adipate) OR (Dibutyl hexanedioate) OR (dibutyl ester adipic acid) OR (1,6-dibutyl ester hexanedioic acid) OR (dibutyl ester hexanedioic acid)

Pubmed, DiBA: (diisobutyl adipate) OR (diisobutyl ester adipic acid) OR (105-99-7)

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 a ratio 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>).