CPSC Staff Statement on University of Cincinnati Report
"Toxicity Review for Diisononyl Adipate (DINA)"[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 DINA follows. Based on the research conducted by the University of Cincinnati, the animal data were sufficient to support the conclusion that DINA does not fit the designation of acutely toxic under the FHSA following single oral or dermal exposures. No data were available on the acute inhalation toxicity of DINA.

[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

Diisononyl adipate

(DINA)

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1 Introduction

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with diisononyl adipate (DINA).

Literature searches for physico-chemical, toxicological, exposure, and risk information were performed in June 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 (June, 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 DINA and synonyms. Downloaded documents were saved as pdfs. Websites searched included:

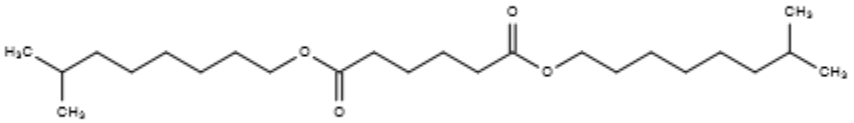
- ANSES Information on Chemicals (https://www.anses.fr/en)
- ChemIDPlus (https://chem.nlm.nih.gov/chemidplus/)
- ECHA Information on Chemicals (https://echa.europa.eu/information-on-chemicals)
- EFSA (https://www.efsa.europa.eu/)
- EPA chemistry dashboard (https://comptox.epa.gov/dashboard)
- EPA Chemview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

Some limited supplemental web searching via Google was conducted in February, 2019.

2 Physico-Chemical Characteristics

Table 1: Physical-Chemical Characteristics and Identity of DINA

Chemical Name	Diisononyl adipate (DINA)
Synonyms	Diisononyl adipate; Diisononyl hexanedioate, diisononyl ester hexanedioic acid; 1,6-diisononyl ester hexanedioic acid; DINA; diisononyl ester adipic acid
CAS Number	33703-08-1
Structure	
Chemical Formula	$C_{24}H_{46}O_4$
Molecular Weight	398.628 g/mol
Physical State	Liquid
Color	Colorless
Melting Point	-60ºC (U.S. EPA, 2019)
Boiling Point	232 – 233ºC (ECHA, 2019)
Vapor Pressure	$2.2x10^{-5}$ mmHg, estimated (Health Canada, 2018)
Water Solubility	$2.2x10^{-4}$ mg/L at 20ºC (Health Canada, 2018)
Log Kow	9.24 (Health Canada, 2018)
Henry's Law	$2.9x10^{-5}$ atm-m^3/mole (Health Canada, 2018)

Flashpoint	210ºC (ECHA, 2019)
Density	0.922 g/cm^3 (ECHA, 2019)
Source	Pubchem (2018), unless otherwise stated

K_{ow} is the octanol-water partition coefficient. Henry's Law is Henry's Law Constant. See Appendix 2 for more details.

ECHA (2018) included several studies of di(2-ethylhexyl)adipate (DEHA) in the DINA 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 DINA. In addition, the total number of carbons in the ester chain is similar for the two compounds (nine in DINA and eight for DEHA). However, because toxicity is often due to the functional groups in a chemical (including branching), and the branch for DEHA is much closer to the ester link than it is for DINA, the toxicity of DINA may more closely resemble that of dibutyl sebacate (DBS), than that of DEHA.

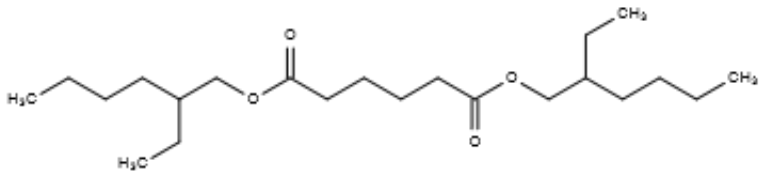


Figure 1. Structure of di(2-ethylhexyl)adipate (DEHA)

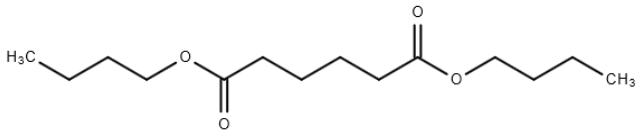


Figure 2. Structure of dibutyl sebacate (DBS)

3 Manufacture, Supply, and Use

Manufacture and Supply

DINA is a high production volume chemical with U.S. manufacture and imports reported between 1 and 10 million pounds (500 to 5,000 tons) per year for 2015 (U.S. EPA, 2019b). DINA is manufactured and/or imported in the European Economic Area at a rate of greater than 100 tons per year (ECHA, 2019).

Use

Primary uses of DINA include low-temperature polyvinyl chloride (PVC) applications and PVC film/wrapping (ECHA, 2012). DINA is a plasticizer that adds flexibility at low temperatures and impact resistance; it has a lower volatility than other plasticizers (Chemceed, 2019). It is approved for use as an indirect additive for food contact substances (FDA, 2019). ECHA (2012, 2019) reported that DINA uses include in lubricants and greases. Consumer exposure could result from DINA use in building and construction materials, electrical and electronic products, furniture and furnishings, personal care products, plastic and rubber products (ECHA, 2019). Bui et al. (2016) reported that DINA is used in skin conditioning agents, emollients, and solvents. DINA is also used by professional workers in metal working fluids and in manufacturing of rubber and plastic products (ECHA, 2019).

U.S. producers/importers have reported that DINA is intended for use in products intended for children (U.S. EPA, 2019b). Its presence has been measured in childcare articles, dolls, and toys (Maag et al., 2010; Abe et al., 2012, 2003).

4 Toxicokinetics

No toxicokinetic information specific to DINA was located.

In a series of GLP-compliant OECD 417 guideline studies, the toxicokinetics of DEHA was investigated in mice, rats, and monkeys (Midwest Research Institute, 1984, as cited by ECHA, 2019). Overall, the data indicated that DEHA was readily absorbed, distributed to various tissues, metabolized, and excreted in urine and to a lesser extent in feces and expired CO_2. Prolonged retention in tissue was minimal.

No standard toxicokinetic studies were reported for DBS, but hydrolysis has been reported *in vitro* by pancreatic lipase and in intestinal fluid to sebacic acid and butanol (Smith, 1953;SCF, 1997, as cited by BIBRA, 1998).

5 Hazard Information

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

BASF (1984a, as cited by ECHA, 2019) tested the acute toxicity of 5000 mg/kg DINA administered via gavage in Wistar rats (5/sex) in a study performed equivalent to OECD Guideline 401. No mortality occurred during a 14-day post-exposure observation period. Details regarding other signs of toxicity were not provided. The LD_{50} was >5000 mg/kg.

In an unpublished report (Anonymous, 1968a, as cited by U.S. EPA, 2019), authors exposed rats (5/dose, sex and strain not provided) to 0, 35, 120, 417, 1450, 5000, or 10,000 mg/kg DINA via

gavage. No deaths or other signs of toxicity occurred during the 14-day observation period. The LD_{50} was >10,000 mg/kg.

5.1.2 Acute Dermal Toxicity

In an unpublished report (Anonymous, 1968b, as cited by U.S. EPA, 2019), authors exposed rabbits (4/dose, sex and strain not given) to 0, 50, 200, 794, or 3160 mg/kg DINA via application to abraded abdominal skin for 24 hours. No deaths or signs of systemic toxicity were seen during the 14-day observation period. Mild redness and swelling was observed during the first week of observation. The dermal LD_{50} was >3160 mg/kg.

5.1.3 Acute Inhalation Toxicity

No studies of acute inhalation toxicity were found.

5.1.4 Irritation/Sensitization

Irritation/corrosion data in rabbits indicate DINA is not irritating. No data from *in vivo* sensitization studies were found, but a citation to a quantitative structure-activity relationship (QSAR) analysis indicated DINA is not expected to be a skin sensitizer.

BASF (1984b, as cited by ECHA, 2019) reported skin irritation/corrosion testing of DINA in Vienna White rabbits (one male and two females treated) according to OECD Guideline 404. About 0.5 mL of undiluted DINA was applied to shaved skin and washed off after 4 hours. No effects were seen over a 72-hour observation period.

BASF (1984c, as cited by ECHA, 2019) also reported eye irritation/corrosion testing in Vienna White rabbits (one male and two females in treatment group) according to OECD Guideline 405. A single application of 0.1 mL undiluted DINA was applied to the conjunctival sac. The only effect observed during the 72-hour observation period was slight irritation of the conjunctivae (mean score for 1-72 hours was 0.83 out of 3), which was fully reversible within the 72-hour period. A brief citation (David et al., 2001 as cited by ECHA, 2019) referred to conjunctival irritation in rabbits that cleared completely within 72 hours. This report noted a Draize score of 8 out of 110, with group mean scores for conjunctival redness of 1.83, 1.0, and 0.17 at 24, 48, and 72 hours, respectively. It is possible this is the same as the above study by BASF (1984c).

In unpublished data (Anonymous, 2018, as cited by ECHA, 2019), the sensitizing potential of DINA was assessed in a QSAR analysis using OASIS TIMES-SS (Tissue Metabolism Simulator for skin sensitization) software v.2.27.19. It was determined that DINA fulfilled the domain requirements of the system, and predictions for skin sensitization potential of DINA were negative.

5.2 Repeated Dose Toxicity

DINA has been investigated in two repeated-dose dietary exposure studies, in rats and dogs. These studies indicate low repeated-dose toxicity via the oral route. The target organs for adverse effects are liver and kidney, accompanied by decreased body weight and food consumption. It is possible that the decreased food consumption was due to poor palatability of feed containing DINA, and the body weight changes may have been secondary to decreased food consumption.

An unpublished report (Anonymous, 1971a, as cited by ECHA, 2019, U.S. EPA, 2019) described a subchronic toxicity study in which rats (10/sex/dose, strain not provided) were given 0, 50, 150, or 500 mg/kg-day DINA in the diet for 13 weeks. The range of endpoints included hematology, blood chemistry, and urinalysis for 5 rats/sex/dose and full clinical and histological examination for all animals. Relative kidney weight, but not absolute kidney weight, was elevated at 500 mg/kg-day. Kidney histology was normal, and the weight change was considered non-adverse by the authors. No other effects were reported and no quantitative results were available. The NOAEL for the study was 500 mg/kg-day, the highest dose tested.

In another unpublished subchronic study (Anonymous, 1971, as cited by ECHA, 2019, U.S. EPA, 2019), DINA was given to beagle dogs (4/sex/dose) in the diet at levels of 0, 0.3 1.0, and 3.0 % for 13 weeks with the high dose escalated to 6.0% at week 9. No reason was available for the dose escalation in the high-dose group. Based on the dose conversion for 1.0% given by U.S. EPA (2019), the corresponding doses were 0, 82, 274, and >822 mg/kg-day. Endpoints evaluated included hematology, blood chemistry, urinalysis, and full clinical and histological examination upon necropsy. Decreased body weight, decreased food consumption, increased liver weights, elevated liver enzymes, and histologic changes in liver and kidneys were seen at the high dose. No further details on the reported effects were provided. Although the decreased food consumption may have been related to poor palatability, in the absence of quantitative data it is not possible to determine whether the decreased body weight was related to decreased food consumption. Nonetheless, the histologic changes in the liver and kidneys can be assumed to be adverse. Because of the dose escalation and change in food consumption in the high-dose group, it is not possible to estimate the mg/kg-day dosage with the information given. The NOAEL cited by ECHA was approximately 274 mg/kg-day.

5.3 Chronic Toxicity/Carcinogenicity

No studies of carcinogenicity were found for DINA.

ECHA (2018) conducted read-across from 2-year feeding studies for the chemical analogue DEHA (NTP, 1982, as cited by ECHA, 2019), in which B6C3F1 mice and F344 rats were given DEHA at doses of 0, 1715, or 3570 mg/kg-day (mice) and 0, 600, or 1250 mg/kg-day (rats). Study designs were equivalent to OECD Guideline 451 in both species. No carcinogenic effects were observed, and the NOAELs were 3570 mg/kg-day in mice and 1250 mg/kg-day in rats.

Smith (1953) found no evidence of carcinogenicity for DBS in 1-year and 2-year studies in rats, but the studies 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. In the 1-year study, male Sprague Dawley rats (10/dose) were treated with DBS in feed at doses of about 0, 6.9, 34.5, 172.5 or 862.5 mg/kg-day, and in the 2-year study, male Sprague Dawley rats (16/dose, 32 control) were treated with DBS in feed at doses of about 0, 6.9, 34.5, 172.5, 862.5, and 4312 mg/kg-day. No treatment-related effects were reported.

5.4 Reproductive Toxicity

No reproductive studies were found for DINA.

ECHA (2018) conducted read-across from a one-generation rat reproductive study conducted equivalent to OECD Guideline 415 with the chemical analogue DEHA (CEFIC, 1988, as cited by ECHA, 2019). The rats were given DEHA in the diet at doses of 0, 28, 170, or 1080 mg/kg-day (0, 300, 1800, and 12,000 ppm in feed). The males were exposed for 10 weeks premating and during mating, and the females were exposed for 10 weeks prior to mating, through mating and gestation, until the end of lactation (postnatal day; PND 22). The offspring were reared to PND 36. A small but statistically significant decrease in body weight gain was seen in parental females and pups at 1080 mg/kg-day, and liver weights were increased in the parental animals. The authors noted the systemic NOAEL as 170 mg/kg-day and the reproductive NOAEL as 1080 mg/kg-day.

FDA (2014) reported on a 1-generation reproductive toxicity study of DBS 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 vehicle with 0, 100, 300, or 1000 mg/kg-day. 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. The FDA identified the high dose of 1000 mg/kg-day as the study NOAEL. There was no mention in the FDA report 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 Sprague Dawley rats (20/sex, 10 controls/sex) with DBS in the diet at about 0 or 4312 mg/kg-day for 10 weeks prior to mating. 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. There was no effect on fertility or on pup survival, but there was a significant decrease in the pup weight at weaning and weight gain at PND 42. The single dose tested of 4312 mg/kg-day (dams) was a developmental LOAEL, but a systemic and reproductive NOAEL.

5.5 Prenatal, Perinatal, and Post-natal Toxicity

No developmental toxicity studies were available for DINA.

ECHA (2018) conducted read-across from a developmental toxicity study consistent with OECD Guideline 414 that was performed with chemical analogue DEHA in rabbits at actual doses of 0, 36, 70, and 145 mg/kg-day (BASF, 2014[1], as cited by ECHA, 2019). The rabbits were treated with DEHA in the diet on days 6 to 29 post-coitum. The maternal and developmental NOAELs provided were both 145 mg/kg-day.

In another study used for a read-across analysis, Dalgaard et al. (2003, as cited by U.S. EPA, 2019) performed a developmental study for DEHA equivalent to OECD Guideline 426. Pregnant rats received 0, 200, 400, or 800 mg/kg-day from gestation day 7 to PND 17, and the LOAEL for developmental toxicity was 400 mg/kg-day based on an increase in post-natal deaths. In the authors' report, the maternal NOAEL was 400 mg/kg-day based on prolonged gestation at 800 mg/kg-day. The developmental NOAEL was 200 mg/kg-day.

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, 2014a). The high dose of 1000 mg/kg-day was the study NOAEL for both maternal and developmental effects.

In another GLP-compliant developmental toxicity study, Hra: (NZW)SPF rabbits (22 pregnant females/dose) were 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, 2014b, as cited by FDA, 2014). 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 at the high dose, 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

DINA was not mutagenic or clastogenic in studies done in bacterial and mammalian cells.

McKee et al. (1986) tested DINA in a gene mutation (Ames) assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. DINA was not mutagenic at levels up to 1000 µg/plate in the presence or absence of exogenous metabolic activation. Another study (BASF, 1984d, as cited by ECHA, 2019) reported an Ames test using the same bacterial strains as above exposed to DINA at up to 5000 µg/plate, with no mutagenicity observed with or without metabolic activation.

McKee et al. (1986) also tested DINA in a mammalian gene mutation assay using L5178Y mouse lymphoma cells. DINA was negative for mutagenic activity at levels up to 92 mg/mL

[1] Cited as Anonymous, 2014 in the DEHA summary (Risk Science Center, 2018)

with or without metabolic activation. Relative total growth was <20% at the top doses, indicating that an adequately high dose was tested.

Clastogenicity was tested in a micronucleus assay that was GLP-compliant and performed according to OECD Guideline 487 (BASF, 2013, as cited by ECHA, 2019). Micronuclei were not increased in V79 Chinese hamster lung fibroblasts following 4 hours exposure at up 1000 µg/mL with or without metabolic activation, nor following 24-hour exposure to up to 1000 µg/mL (without activation).

McKee et al. (1986) tested DINA in two morphological transformation assays using mammalian cells. DINA did not induce morphological transformation in ex vivo Syrian hamster embryonic cell colonies at levels up to 1000 µg/mL or BALB/3T3 clone A31 cell line colonies at levels up to 1200 µg/mL.

5.7 Mechanistic Studies

There are no available mechanistic studies of DINA.

5.8 Mode of Action

No data are available on the mode of action of DINA. However, the structurally-related chemical DEHA is known to cause liver effects via peroxisome proliferation (Lake et al., 1997), and so it is plausible that DINA also causes at least some effects via peroxisome proliferation.

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

The oral toxicity of DINA appears to be low, but the conclusions are limited by the small number of available studies, and minimal reporting for those studies.

The only available repeat dose studies involved exposures for 13 weeks. In rats, a non-adverse increase in relative kidney weight was observed at 500 mg/kg-day in diet, with no effects on kidney histology, absolute kidney weight, clinical chemistry, or urinalysis (Anonymous, 1971a, as cited by ECHA, 2019, U.S. EPA, 2019). In dogs, undefined histopathological changes were reported in the kidneys after exposure to 3% in feed for 8 weeks and 6% in feed for 5 weeks (estimated dose >822 mg/kg-day, NOAEL = 272 mg/kg-day) (Anonymous, 1971b, as cited by ECHA, 2019, U.S. EPA, 2019).

The 13-week dog study also reported increased liver weight, elevated liver enzymes, and “histopathological changes” in the liver at the high dose (estimated dose >822 mg/kg-day, NOAEL = 272 mg/kg-day). The first two changes could be attributable to peroxisome proliferation. Without additional information about the nature of the histopathological changes, it cannot be determined whether they could be due to peroxisome proliferation (e.g., hepatocellular hypertrophy), or whether these changes indicate an adverse effect.

Decreased body weight and decreased food consumption were also seen in the dog study at the high dose (estimated at >822 mg/kg-day). Without further details, it is not clear whether these changes reflect and adverse effect or poor palatability of the diet.

DINA has not been tested for reproductive or developmental toxicity.

DINA has not been tested for carcinogenicity. However, DINA was consistently negative for gene mutation in bacterial and mammalian cells and for clastogenicity in mammalian cells (McKee et al., 1986; BASF, 1984d, 2013, as cited by ECHA, 2019).

5.10 Uncertainties and Data Gaps

Database:

The data gaps for DINA are fairly substantial, although read-across from DEHA can aid in filling some of the gaps.

Toxicokinetic data are not available for DINA, although the observation of systemic effects in rats and dogs following subchronic exposure indicates that absorption does occur to a meaningful degree. Aside from acute studies, data are available only via the oral route. For the acute duration, there are data gaps for acute inhalation and for sensitization, although QSAR analysis indicated that DINA is not expected to be a sensitizer (Anonymous, 2018, as cited by ECHA, 2019).

Subchronic studies are available for DINA in the rat (Anonymous, 1971a, as cited by ECHA, 2019, U.S. EPA, 2019) and dog (Anonymous, 1971b, as cited by ECHA, 2019, U.S. EPA, 2019). However, neither study was reported as being conducted according to test guidelines, and only limited information on these studies are available, all from secondary sources. Furthermore, the testing does not appear to have been conducted to sufficiently high doses to fully characterize the toxic potential of DINA.

No data on the reproductive or developmental toxicity of DINA are available.

Data on carcinogenicity are also lacking. However, DINA is not expected to be carcinogenic, in light of the lack of carcinogenicity of the analogue DEHA, as well as the negative results for DINA for gene mutation in bacterial and mammalian cells and for clastogenicity in mammalian cells (McKee et al., 1986; BASF, 1984d, 2013, as cited by ECHA, 2019).

Hazard:

Body weight: It is unclear whether the decreased body weight in the dog study (Anonymous, 1971b, as cited by ECHA, 2019, U.S. EPA, 2019) is secondary to decreased food consumption, and whether decreased food consumption can be attributed to poor palatability.

Liver and kidney changes: The toxicological significance of the histopathological changes in the liver and kidney reported in the dog study (Anonymous, 1971b, as cited by ECHA, 2019, U.S. EPA, 2019) is unclear, in the absence of a more complete description of those changes.

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

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[2]	Toxicological Basis	Comments
Unknown strain, rat (M & F) 10/sex/dose Anonymous, 1971a, as cited by ECHA, 2019, U.S. EPA, 2019	13 weeks Diet 0, 50, 150, or 500 mg/kg-day	Kidney	NOEL = N/A LOEL = 500 (M,F)	Non-adverse increase in relative kidney weight, kidney histology was normal and absolute weight unchanged.	Endpoints included hematology, blood chemistry, and urinalysis for 5 animals. Full clinical and histological examination was done on all animals. Limited details available
Beagle dogs (M & F) 4/sex/dose Anonymous, 1971b, as cited by ECHA, 2019, U.S. EPA, 2019	13 weeks Diet 0, 0.3, 1.0, or 3.0-6.0% 0, 82, 272, and >822 mg/kg-day	Body Weight	NOAEL = 272 (M,F) LOEL = >822 (M,F)	Decreased body weight and food consumption	Endpoints included hematology, blood chemistry, urinalysis, clinical observation, and histological examination of a broad range of organs. The high dose group was escalated from 3.0% to 6.0% on week 9. Dose conversions based on extrapolation from mg/kg estimate at the NOAEL. Dose conversion of the high-dose group is not possible due to inconsistent dose and dose-related feeding behavior.
		Liver	NOAEL = 272 (M,F) LOAEL = >822 (M,F)	Increased liver weight, elevated liver enzymes, histopathological changes, not further described	
		Kidney	NOAEL = 272 (M,F) LOAEL = >822 (M,F)	Histopathological changes, not further described	

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

6 Exposure

The use of DINA in consumer products has been described in Section 3 of this report. The general population may be exposed to DINA via ingestion of foods into which DINA has migrated from the packaging or from PVC films used for food packaging. Consumers may be exposed dermally through use of DINA-containing lubricants and greases used in vehicles or machinery (ECHA, 2019). Dermal contact with toys or consumer products may also be a route of exposure. Infants and children may be exposed via mouthing of products (e.g., children's toys) containing DINA.

Toys and childcare products are a potential source of exposure to DINA. A 2007 survey of toys and childcare products in Germany, Austria, and Switzerland (252 samples from 172 items) found DINA in 4% of the tested materials, with a mean concentration of 20% DINA (Biedermann-Brem et al., 2008, as cited by Maag et al., 2010). Another survey in 2007 in the Netherlands found DINA in 6% of the tested toys and childcare products (FCPSA 2008, as cited by Maag et al., 2010). Abe et al. (2003, 2012) measured plasticizers in PVC toys in Japan. DINA was detected in 25% of the soft toys (N=30) purchased in fiscal year 2000, with an average concentration of 114 mg/g. In the following year, DINA was detected in 25% of the soft toys (N=66) purchased, with an average concentration of 86 mg/g (Abe et al., 2003). In a more recent study of 101 samples of PVC toys, DINA was detected in 22% of the "designated toys"[3] samples (mean concentration [detected samples only] of 11%), and in 5% of the "not-designated" toys samples (mean concentration [detected samples only] of 4.4%) (Abe et al., 2012). No information was located on estimated doses from toys or childcare products.

Food is another potential exposure source. Carlos et al. (2018) analyzed 56 food contact materials from domestic and international sources purchased in Maryland, to identify and quantify their primary plasticizers. Of seven food service wraps evaluated, four were made of PVC, and DINA was the primary plasticizer in one of the four wraps, with a concentration of 13.1% (SD 3.5). Studies in Japan have found that DINA migrates from PVC film wrapping to foods. Hirayama et al. (1991) investigated the migration of adipate plasticizers from PVC food films into various food and observed that DINA tended to migrate more from foods cooked with oil, than raw fish, meat, and vegetables. Saito et al. (2002) measured DINA in 50 processed foods in Japan; levels ranged from not detected (<0.005) to 20.2 mg/kg. The authors presumed that the high levels of DINA found in fish paste products, fried croquettes, and fried dumplings were due to migration from plasticized food wrappings. Migration of DINA from fried croquettes decreased with internal temperature of the croquettes and standing time after frying (before wrapping the croquette). DINA has also been measured in two of four PVC food contact

[3] 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.

gloves examined and was found to be present at 23% and 25%, respectively (Kawamura et al., 2002).

Kawamura et al. (2017) investigated the migration of DINA from PVC food films purchased in Japan in 1999, and used the data to estimate daily intake. Migration of DINA from film to food and food simulants ranged widely from 0.01% to 95%; the highest migration levels were into lipid-soluble simulants, oil, and fatty foods. The percent migration varied by heating conditions and time, for example), 8% for hot croquettes (heated 30 minutes), and 11% in microwaved croquettes (20-60 seconds after boiling). The authors estimated a daily intake of DINA from these films (for the time period around the year 2000) of 21 µg/kg-day.

In a study using Japanese hospital diets, daily intakes of various plasticizers were calculated based on a one-week duplicate diet from three hospitals in Japan (Tsumura et al., 2003). The average daily intake of DINA from one hospital was much greater than the other two (1338 µg/day, versus 27 µg/day and 18 µg/day for the other two hospitals). The authors suggested that plastic items involved with food preparation and storage contributed to the level of plasticizers in the foods.

7 Discussion

7.1 Toxicity Under FHSA

Animal data were sufficient to support the conclusion that **DINA 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 or dermal exposures. Acute oral LD_{50} values for DINA in rats were >5000 mg/kg (BASF, 1984a, as cited by ECHA, 2019; Anonymous, 1968a, as cited by U.S. EPA, 2019). The acute dermal LD_{50} for DINA in rabbits was >3160 mg/kg (Anonymous, 1968b, as cited by U.S. EPA, 2019). No data were available on the acute inhalation toxicity of DINA.

DINA did not cause skin irritation or eye in rabbits in guideline-compliant studies BASF (1984b, 1984c, as cited by ECHA, 2019). No data were available on the sensitization potential of DINA, but QSAR analysis indicated that DINA is not expected to be a sensitizer (Anonymous, 2018, as cited by ECHA, 2019).

A subchronic study in dogs suggests that DINA can cause effects on body weight, as well as on the liver and kidney (Anonymous, 1971b, as cited by ECHA, 2019, U.S. EPA, 2019). However, an independent evaluation of the adversity of the observed changes is not possible, due to the limited study reporting.

No data on the reproductive or developmental toxicity of DINA are available.

Data on carcinogenicity are also lacking, although DINA is not expected to be carcinogenic, in light of the lack of carcinogenicity of the analogue DEHA, as well as the negative results for

DINA for gene mutation in bacterial and mammalian cells and for clastogenicity in mammalian cells (McKee et al., 1986; BASF, 1984d, 2013, as cited by ECHA, 2019).

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APPENDIX 1

Search Terms Used

Toxline	"Diisononyl adipate" OR (Diisononyl hexanedioate) OR (Diisononyl hexanedioate) OR (diisononyl ester hexanedioic acid) OR (1,6-diisononyl ester hexanedioic acid) OR (diisononyl ester adipic acid) OR (33703-08-1)
Pubmed	(Diisononyl adipate) OR (Diisononyl hexanedioate) OR (diisononyl ester hexanedioic acid) OR (diisononyl ester adipic acid) OR (33703-08-1)

APPENDIX 2

Explanation of Physico-chemical Parameters

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 (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).