UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
Bethesda, MD 20814

Memorandum

Date: October 25, 2010

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SUBJECT : Toxicity Review of **Diundecyl phthalate (DUP)**

The following memo provides the Versar Inc. and SRC, Inc. contractor's and U.S. Consumer Product Safety Commission's (CPSC's) Health Sciences staff assessment of the potential toxicity associated with **DUP.**

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 illness or injury during or as a result of reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards under the FHSA (CPSC, 1992; summarized at 16 CFR 1500.135)

The FHSA addresses both acute and chronic hazards. While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic health hazards, the manufacturer is required to label a product appropriately according to the requirements of the FHSA. The first step in the risk assessment process is hazard

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identification, that is, a review of the available toxicity data for the chemical under consideration and a determination of whether the chemical is considered “toxic”. Chronic toxicity data (including carcinogenicity, neurotoxicity, and reproductive and developmental toxicity) are assessed by the CPSC staff using guidelines issued by the Commission (CPSC, 1992). If it is concluded that a substance is “toxic” due to chronic toxicity, then a quantitative assessment of exposure and risk is performed to evaluate whether the chemical may be considered a “hazardous substance”. This memo represents the first step in the risk assessment process; that is, the hazard identification step.

FINAL

TOXICITY REVIEW FOR DIUNDECYL PHTHALATE (DUP, CASRN 3648-20-2)

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TABLE OF CONTENTS

TOXICITY REVIEW FOR DIUNDECYL PHTHALATE (DUP)

APPENDICES

LIST OF TABLES

LIST OF ABBREVIATIONS AND ACRONYMS

ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
DUP	Diundecyl phthalate
GLC	Gas-liquid chromatography
HMWPEs	High molecular weight phthalate esters
NOAEL	No-observed-adverse-effect level
LOAEL	Lowest-observed-adverse-effect level
LC_{50}	Lowest concentration (50)
LD_{50}	Lowest dose (50)
SE	Standard error

EXECUTIVE SUMMARY

DUP is a moderate use plasticizer found in a variety of consumer products.

Exposure to DUP resulted in an oral LD_{50} > 15,800 mg/kg, a dermal LD_{50} > 7,900 mg/kg, and an inhalation LC_{50} of >1.8 mg/L in inadequately described rat, rabbit, and rat studies, respectively. No dermal irritation was noted in a human skin patch study and two rabbit studies. An additional rabbit study reported no to mild irritation following exposure to DUP. No to minimal eye irritation was reported in two rabbit ocular studies. No dermal sensitization was reported in a human skin patch study.

Evidence supported the conclusion that DUP was a subchronic toxicant. Exposure to DUP induced decrements in body weight, increases in relative liver weight, histopathology, and liver enzymes, and decrements in testicular weight, sperm count and motility.

Acceptable daily intakes values (ADI's) are calculated when a given chemical is considered "toxic" and sufficient toxicity information is available. The ADI is the amount of a chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers.

ADI's were not estimated for DUP relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data (additional studies) on toxicological endpoints were not available. Even though NOAELs and LOAELs could be described for particular studies, the lack of supporting studies suggests that there was "inadequate evidence" for the designation of DUP as a "chronic hazard" when considering FHSA criteria (16 CFR §1500.135).

TOXICITY REVIEW FOR DIUNDECYL PHTHALATE (DUP, CASRN 3648-20-2)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with Diundecyl phthalate (DUP). This assessment was prepared from a variety of review articles (NICNAS, 2008; EPA, 2010; HSDB, 2009; ECB, 2000) as well as supplemental independent studies retrieved from literature searching.

Historically, concerns regarding most phthalates have been primarily associated with their potential to induce adverse reproductive/developmental effects in humans (NICNAS, 2008). The structural and physicochemical properties of certain phthalates that allow migration and leaching out of products, especially soft plastics, have also been a concern (NICNAS, 2008).

2. IDENTITY AND PHYSICOCHEMICAL CHARACTERISTICS

This section highlights the identity and key physicochemical properties of DUP.

DUP is comprised of a pair of 11-carbon esters linked to a benzene-dicarboxylic acid ring. The branched ester side chains are in an *ortho* configuration, in contrast to those found in isophthalates (*meta*) or terephthalates (*para*).

DUP is currently considered to belong to the High Molecular Weight Phthalate Esters (HMWPE) group.

The identity and physicochemical properties of DUP can be seen in Tables 2.1 and 2.2 (NICNAS, 2008; HSDB, 2009; ECB, 2000).

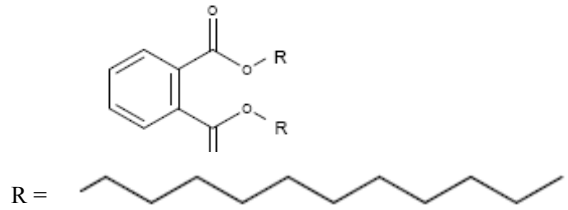
Table 2.1 Names, Structural Descriptors, and Molecular Formulas of DUP (NICNAS, 2008)	
CAS Number:	3648-20-2
Chemical Name:	1,2-Benzenedicarboxylic acid, diundecyl ester
Common Name	Diundecyl phthalate (DUP)
Molecular Formula:	C30H50O4
Structural Formula:	 R =
Molecular Weight:	474.7 (based on a di-C11 phthalate ester)
Synonyms:	Phthalic acid, diundecyl ester; Undecyl alcohol, phthalate
Purity/Impurities/Additives:	Purity: >99.5% w/w Impurity: 0.1-0.2% w/w antioxidant Additives: None

Table 2.2 Physicochemical Properties of DUP (NICNAS, 2008)	
Property	**Value**
Physical state	Colorless oily liquid (NICNAS, 2008); Crystals from ethanol (HSDB, 2009)
Melting point	-9°C (NICNAS, 2008); 35.5°C (HSDB, 2009)
Boiling point	501°C (101.3 kPa; NICNAS, 2008; ECB, 2000)
Density	954 kg/m^3 (NICNAS, 2008)
Vapor pressure	4.97 x 10^{-10} kPa (25°C; NICNAS, 2008); 1.22 x 10^{-9} mm Hg (25°C; HSDB, 2009)
Water solubility	4.41 x 10^{-9} g/L (NICNAS, 2008); 1.11 mg/L (20°C; HSDB, 2009)
Partition coefficient n-octanol/water (log Kow)	10.3 (25°C; NICNAS, 2008) ; 11.49 (estimated; HSDB 2009); 10.33-11.49 (25°C; ECB, 2000)
Henry's law constant	5.60 x 10^{-5} atm-cu m/mol (25°C; HSDB 2009)
Flash point	Not available

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

In general, DUP is manufactured commercially in a closed system by catalytically esterifying phthalic anhydride with undecanol. As with other phthalates, the unreacted alcohols are recovered and reused, and the DUP mixture is purified by vacuum distillation or activated charcoal. The purity of DUP can achieve 99% or greater using current manufacturing processes (NICNAS, 2008). DUP is also manufactured as a mixture of branched chain isomers. The remaining fraction of the DUP commercial mixture can contain 0.1-0.2 wt% of anti-oxidants such as 1,1,3-Tris (2-methyl-4-hydroxy-5-tert-butylphenyl) butane (Topanol CA; NICNAS, 2008; ExxonMobil, 2001), and a maximum of 0.1% water (BASF, 2009)

DUP is currently marketed by BASF (Palatinol®111P-I; produced by Sterling at Texas City) and ExxonMobil (Jayflex L11P, L11P-E).

Supply

U.S. production of DUP has been slowly increasing since the implementation of chemical tracking in 1982 (8,000 metric tons to 18-20,000 metric tons in mid 2000's). Currently, U.S. production of DUP is reported as 18,000 metric tons (2008) and is projected to increase to 20,200 metric tons (2013). DUP's proportion of the total phthalate production market (3.1%) is also projected to increase (to 3.6%) during the same period (+2.3% growth rate; Bizzari et al. 2009). The 2008 estimate is slightly down from 20,000 metric tons reported in 2005 (3.3% of phthalate production market; Bizzari et al. 2007).

U.S. consumption of DUP has paralleled production estimates. Current consumption of DUP has been reported as 17,500 metric tons (2008) and is projected to increase to 19,200 metric tons (2013). DUP's proportion of the total phthalate consumption market (2.9%) is also projected to increase (to 3.3%) during the same period (+1.9% growth rate; Bizzari et al. 2009).

In the past 20 years, U.S. consumption (in metric tons) of DUP has been within a metric ton or two less than production estimates, and currently, percentages of total phthalate consumption market are similar to production. This suggests that most DUP produced in the U.S. is utilized locally and a small amount may be exported.

Use

The high molecular weight phthalate esters are used primarily as industrial chemicals that are associated with polymers to impart flexibility in polyvinyl chloride (PVC) resins. They are also used as synthetic base stocks for industrial lubricating oils (NICNAS, 2008). DUP is used for applications that require low fog and low temperature flexibility. Generally, this includes wiring and cable jacketing and insulation, furniture and automobile upholstery, floor mats, and seat covers, flooring, wall coverings, coil coatings, pool liners, water stops, roofing membranes, and coated fabrics (NICNAS, 2008; ExxonMobil, 2001). DUP has also been used as a non-PVC polymer in thermoplastics (i.e. flame retardant nylon), rubbers, paints and adhesives (NICNAS, 2008) and can be blended with trimellitate plasticizers.

4. TOXICOKINETICS

No relevant toxicokinetic data were located for DUP.

5. HAZARD INFORMATION

This section contains brief hazard summaries of the adverse effects of DUP in a variety of animal and bacterial species. More detailed discussions of the studies can be viewed in the Appendices. When evaluating hazard study data, Consumer Product Safety Commission (CPSC) staff utilized the definitions for toxicity as presented in regulations (16 CFR §1500.3(c)(2)(ii)) and the chronic hazard guidelines (16 CFR §1500.135) in the Federal Hazardous Substances Act (FHSA; 15 U.S.C. 1261-1278). When considering the FHSA, substances that are "known" or "probable" toxicants are "toxic" and substances that are considered "possible" toxicants are "not toxic" (Table 5.1).

Table 5.1. Classification of Chronic Hazards (as per the FHSA)

Evidence	Human Studies	Animal Studies
Sufficient evidence	**Known**	**Probable**
Limited evidence	**Probable**	Possible
Inadequate evidence	Possible	—

Exposure to DUP resulted in an oral LD_{50} > 15,800 mg/kg, a dermal LD_{50} > 7,900 mg/kg, and an inhalation LC_{50} of >1.8 mg/L in inadequately described rat, rabbit, and rat studies, respectively. No dermal irritation was noted in a human skin patch study and two rabbit studies. An additional rabbit study reported no to mild irritation following dermal exposure to DUP. No to minimal eye irritation was reported in two rabbit ocular studies. No dermal sensitization was reported in a human skin patch study.

Evidence supported the conclusion that DUP was a subchronic toxicant. Exposure to DUP induced decrements in body weight, increases in relative liver weight, histopathology, and liver enzymes, and decrements in testicular weight, sperm count and motility.

Acceptable daily intakes values (ADI's) are calculated when a given chemical is considered "toxic" and sufficient toxicity information is available. The ADI is the amount of a chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers. ADI's were not estimated for DUP relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data (additional studies) on toxicological endpoints were not available.

In the following discussions, hazard information was divided into sections thought to be of interest for regulatory matters (i.e., for labeling and other mitigation measures) as well as for

biological and pathological consistency. More specifically, hazards were divided into whether the exposure was singular or repeated. Hazards associated with repeated exposures were further divided into groupings based on the affected organ system (i.e., hepatic, neurological, hematologic, etc.) and discussed in terms of the exposure duration if sufficient information existed to do so (***acute***, ≤14 days; ***intermediate-term*** or ***subchronic***, 15–364 days; ***long-term*** or ***chronic***, ≥365 days; and ***multigenerational***; ATSDR, 2007) where appropriate. Discrete study information can be reviewed in the Appendices.

ACUTE DOSE TOXICITY

5.1. Acute Oral Toxicity

Citing unpublished work from Birch (1951), Krauskopf (1973) stated that a single oral dose of 15.8 g/kg of DUP was nonlethal and practically nontoxic to rats. No further information was provided.

The lack of methodological information and corroboration on the acute oral toxicity for DUP can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of DUP as "acutely toxic" via oral exposure under the FHSA (16 CFR §1500.3(c)(2)(i)(A)).

5.2. Acute Dermal Toxicity

An acute dermal LD_{50} value of >7.9 g/kg has been reported for DUP in rabbits (David et al., 2001; ECB, 2000). No further information is available.

The lack of methodological information and corroboration on the acute dermal toxicity for DUP can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of DUP as "acutely toxic" via dermal exposure under the FHSA (16 CFR §1500.3(c)(2)(i)(C)).

5.3. Acute Inhalation Toxicity

No deaths were reported among rats exposed to a saturated atmosphere of DUP vapor for 6 hours, suggesting a 6-hour LC_{50} value of >1.8 mg/L for DUP vapors in rats (the maximum

attainable vapor concentration at ambient temperature) (NICNAS, 2008; David et al., 2001; ECB, 2000). No further details were provided.

The lack of methodological information and corroboration on the acute inhalation toxicity for DUP can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of DUP as "acutely toxic" via inhalation under the FHSA (16 CFR §1500.3(c)(2)(i)(B)).

5.4. Primary Skin Irritation

Information regarding irritation in humans is available in a report by Medeiros et al. (1999). An unspecified amount of undiluted DUP (>99% purity) was applied to the skin of 14 male and 1 female volunteers in a nonwoven cotton pad that was covered and secured to the skin for 24 hours. Evaluations were performed 30 minutes and 24 hours after patch removal. Examination of the application site showed no significant irritation.

Application of 0.5 mL of DUP (purity not reported) to an intact clipped 1 square inch area of the skin of 6 male albino rabbits under occlusion for 24 hours resulted in mild to no skin irritation; observations were recorded at the time the cover was taken off and also 24 hours later (E.I. Dupont de Nemours, 1974). DUP did not act as a primary irritant in New Zealand rabbits following intradermal injection of 0.2 mL undiluted (ECB, 2000; Lawrence et al., 1975, 1971), but few details were provided. Monsanto (1982, as cited in NICNAS, 2008) reported that DUP was non-irritating to the skin of rabbits with a Primary Irritation Index of 0 on a scale from 0 to 8.

Dermal irritation was not noted in a human study and minimal dermal irritation (at most) was noted in animal studies. The estimated "scores" from these studies are expected not to exceed five, the threshold for defining a skin irritant in the FHSA (16 CFR §1500.3(c)(4)).

The weight of evidence including sufficient human and animal data supported the conclusion that DUP did not fit the definition of "corrosive" as outlined in the FHSA (16 CFR §1500.3(c)(3)) or a "primary irritant" when considering FHSA criteria (16 CFR §1500.3(c)(4)).

5.5. Primary Eye Irritation

DUP was not irritating to the eye in rabbits observed for 48 hours following ocular instillation of 0.1 mL undiluted, but few details were provided (ECB, 2000; Lawrence et al., 1975, 1971). Monsanto (1982, as cited in NICNAS, 2008) reported that DUP caused minimal eye irritation to the eyes of rabbits, with a Draize score of 4 on a scale from 0 to 110.

The weight of evidence including sufficient animal data supported the conclusion that DUP did not fit the definition of an ocular "corrosive" as outlined in the FHSA (16 CFR §1500.3(c)(4)).

The lack of additional methodological information on the ocular irritant properties of DUP can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of DUP as an ocular "primary irritant" when considering FHSA criteria (16 CFR §1500.3(c)(3)).

5.6. Sensitization

DUP has been tested as a potential skin sensitizer in humans (Medeiros et al., 1999). One hundred and four volunteers had 0.2 mL of undiluted DUP (>99% pure) applied in a pad to the deltoid region of the arms; pads were held secure with an occlusive hypoallergenic tape. Induction was conducted by applying the test material 9 times to the same site (3 times/week for 3 consecutive weeks), each time for 24 hours. After a 10–17-day rest period, the challenge phase was conducted by applying the test material for 24 hours to a naive site. There was no evidence of dermal irritation during the induction or challenge phases of the study.

A sufficient weight of human evidence suggests that DUP does not fit the definition of a "strong sensitizer" as defined in the FHSA (16 CFR §1500.3(c)(5)).

REPEAT DOSE TOXICITY

5.7. General Effects (Clinical Signs/Food/Water Consumption, Body Weight)

No treatment-related behavioral variations or clinical signs of toxicity were observed in male or female rats fed diets containing up to 2.5% DUP (2,495 mg/kg-day in males and 2,115 mg/kg-day in females) for 21 days (Barber et al., 1987; Chemical Manufacturers Association, 1985). Body weight gain was slightly reduced in high-dose males and mid- and high-dose females, with no significant changes in food intake in either sex. Mean body weight was statistically significantly ($p < 0.05$) lower than controls in high-dose males and in mid- and high-dose females from day 7 on; differences with controls were >10% only in high-dose males during the latter portion of the study (13–15%). Although not statistically significant, a decrease in body weight was also seen in mid-dose males (approximately 5% at study termination; see Table 5.1).

Table 5.2. Necropsy Body Weights in Fischer 344 rats Exposed to DUP for 21 Days

Dose (mg/kg-day)	Necropsy Body Weight (g)
Males	
0	222 ± 4.5[a]
285	224 ± 5.6
1,183	211 ± 3.1 (-5%)
2,495	194 ± 4.5 (-13%)[b]
Females	
0	144 ± 1.5
279	141 ± 3.4
1,106	134 ± 1.3 (-7%)[b]
2,115	133 ± 2.4 (-8%)[b]

[a]Mean ± standard error (SE) for groups of five rats (percentage of change from control).
[b]$p < 0.05$.
Source: Chemical Manufacturers Association (1985).

A repeated-dose gavage study observed no mortality and no clinical signs other than salivation immediately after dosing in male Sprague-Dawley rats (6/group) dosed with 0 (vehicle control) or 500 mg DUP/kg-day by gavage in corn oil for 4 weeks (Kwack et al., 2009). Neither food consumption nor body weight was significantly altered by treatment with DUP in this study.

5.8. Hepatic Effects

The 21-day rat feeding study included evaluation of liver effects by serum chemistry; liver weight; gross, histological and ultrastructural pathology; and biochemical assays for protein and enzyme levels in the liver (Barber et al., 1987; Chemical Manufacturers Association, 1985). Serum triglycerides were significantly reduced ($p < 0.001$) in mid- and high-dose males (approximately 52% in both groups) and so was cholesterol (33% in mid-dose males, $p < 0.01$; 35% in high-dose males, $p < 0.001$). No significant serum chemistry effects were observed in females. Both absolute and relative liver weights were increased in mid- (24 and 23%) and high-dose males (14 and 25%) and in mid- (33 and 34%) and high-dose females (50 and 63%) (Table 5.2). Gross abnormalities observed in the liver of mid- and high-dose rats included pale and/or thickened liver in 3/5 mid-dose males and 2/5 high-dose males, and enlarged and/or darkened liver in 1/5 mid-dose females and 1/5 high-dose females.

Table 5.3. Significant Changes in Liver Weights in Fischer 344 rats Exposed to DUP for 21 Days

Dose (mg/kg-day)	Liver	
	Absolute (g)	Relative (g/100g Body Weight)
Males		
0	7.24 ± 0.21[a]	3.26 ± 0.10
285	8.05 ± 0.41	3.59 ± 0.10
1,183	8.94 ± 0.40 (+24%)[b]	4.24 ± 0.18 (+23%)[b]
2,495	8.42 ± 0.35 (+14%)[b]	4.34 ± 0.09 (+25%)[b]
Females		
0	4.36 ± 0.07	3.02 ± 0.06
279	4.48 ± 0.11	3.18 ± 0.06
1,106	5.80 ± 0.24 (33%)[b]	4.32 ± 0.15 (43%)[b]
2,115	6.53 ± 0.36 (50%)[b]	4.92 ± 0.23 (63%)[b]

[a]Mean ± SE for groups of 5 rats (% change from control).
[b]$p<0.05$
Source: Chemical Manufacturers Association (1985).

Table 5.3 shows the results of histological examination of the liver (Barber et al., 1987; Chemical Manufacturers Association, 1985). The incidences of liver lesions (slight necrosis, slight/moderate vacuolation) were significantly increased in mid- and high-dose males. The degree of cytoplasmic basophilia was decreased in mid- and high-dose males and females. The researchers considered this change in cytoplasm staining characteristics to likely reflect a change in the organelle component and metabolic status of the cell, and noted that similar changes

produced by other compounds were associated with increases in smooth endoplasmic reticulum and associated structures. Ultrastructural examination of the liver confirmed that there was a marked increase in fatty vacuolation and distension of smooth and rough endoplasmic reticulum in high-dose males and revealed an overall moderate proliferation of peroxisomes in the periportal and centrilobular areas in high-dose males and females; low- and mid-dose rats were not examined.

Table 5.4. Incidence of Histological Liver Changes in Fischer 344 rats Exposed to DUP in the Diet for 21 Days

	Males				Females			
Dose (mg/kg-day)	**0**	**285**	**1,183**	**2,495**	**0**	**279**	**1,106**	**2,115**
Reduced cytoplasmic basophilia	0/5	0/5	5/5[a]	5/5[a]	0/5	0/5	4/5[a]	5/5[a]
Slight increase individual cell necrosis	0/5	0/5	4/5[a]	5/5[a]	0/5	0/5	0/5	0/5
Slight cell vacuolization	0/5	0/5	2/5	4/5[a]	1/5	0/5	0/5	0/5
Moderate cell vacuolization	0/5	0/5	5/5[a]	3/5	0/5	0/5	0/5	0/5

[a] $p < 0.05$ (Fisher's exact test conducted by for this review).
Source: Chemical Manufacturers Association (1985).

Biochemical analyses showed increases in liver enzymes and total hepatic protein, consistent with peroxisome stimulation. Cyanide-insensitive palmitoyl-CoA oxidation levels had dose-related increases in both sexes that were statistically significant ($p < 0.001$) in mid- and high-dose males and females. Lauric acid 11- and 12-hydroxylase activities were significantly increased ($p < 0.01$) in males at all dose levels and in high-dose females. Total hepatic protein concentrations were significantly increased ($p < 0.01$) in mid- and high-dose females, but there were no significant changes in total hepatic protein in males or microsomal protein level in either sex. Based on increased absolute and relative liver weight in both sexes and increased incidence of liver lesions in males, the lowest-observed-adverse-effect level (LOAEL) for hepatotoxicity in this study is 1.3% (1,183 and 1,106 mg/kg-day in males and females, respectively) and the no-observed-adverse-effect level (NOAEL) is 0.3% (285 and 279 mg/kg-day, respectively).

A study that compared parameters measured in the Chemical Manufacturers Association (1985) study with similar parameters measured in studies for another 8 plasticizers constructed a quantitative index for peroxisome proliferation (Lin, 1987). The ranking in order of decreasing potency was: di(2-ethylhexyl) phthalate, di(isodecyl) phthalate, di(isononyl) phthalate, di(n-butyl) phthalate, di(ethylhexyl) adipate, DUP, butyl benzyl phathalate, 711 phthalate, and 610 phthalate. The investigator also calculated a statistically predicted dosage that would protect

99 and 99.9% of rats against peroxisome proliferation. These doses were 57.1 and 35.0 mg/kg for DUP, respectively. For the purpose of comparison, the corresponding doses for DEHP were 8.76 and 1.19 mg/kg.

The 4-week rat gavage study (Kwack et al., 2009) included only a limited evaluation of hepatic effects. Serum chemistry and liver weight were monitored, but no pathology examinations were performed. Serum chemistry analyses showed significant increases in total protein (9.1% over control), aspartate aminotransferase (AST, 50% over control), and alkaline phosphatase (ALP, 81% over control). Relative liver weight was increased eighteen percent, but this difference was not statistically significant. The single dose level of 500 mg/kg-day used in this study is a LOAEL for liver effects, based on increases in weight and serum chemistry endpoints suggestive of a toxic effect on the liver (increased AST). A NOAEL was not identified.

The weight of evidence from the above studies supported the conclusion that there was "sufficient animal evidence" for the designation of DUP as a "hepatotoxicant".

5.9. Reproductive Toxicity

Relative testis weight was increased in mid- (8%) and high-dose (15%) males in the 21-day rat feeding study (Barber et al., 1987; Chemical Manufacturers Association, 1985). However, absolute testis weight did not differ from controls. There were no treatment-related histological abnormalities in the testis. These findings suggest that the increase in relative testis weight reflects the decrease in body weight observed in these animals rather than a specific effect on the testis.

The 4-week rat gavage study by Kwack et al. (2009) found no effect on epididymis weights. The relative testis weight was decreased thirteen percent, but this difference was not statistically significant. This study did not include pathology examination, but sperm count and motility analyses were performed. Specific motility parameters measured included percentage of motile sperm, average path velocity, straight-line velocity, curvilinear velocity, amplitude of the lateral head displacement, beat cross frequency, straightness, and linearity. Treatment with DUP significantly reduced both sperm count (28%) and motility (63%). Specific motility parameters significantly reduced were curvilinear velocity (17%), straightness (19%), and linearity (19%). The single dose level of 500 mg/kg-day used in this study is a LOAEL for reproductive effects in

males, based on decreased testis weight and reduced sperm count and motility. A NOAEL was not identified.

The weight of evidence from the above studies supported the conclusion that there was "limited animal evidence" for the designation of DUP as a "reproductive toxicant".

5.10. Prenatal, Perinatal, and Post-natal Toxicity

No developmental toxicity studies were located for DUP.

5.11. Carcinogenicity

Genotoxicity

DUP (purity not reported) was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 when incubated in concentration up to 10 mg/plate with or without metabolic activation (Zeiger et al., 1985). DUP (purity not reported) was negative in an in vitro L5178Y cell mouse lymphoma assay when incubated in concentrations up to 10 µL/mL without metabolic activation, and up to 8 µL/mL with metabolic activation (Barber et al., 2000). In the same study, DUP in concentrations up to 40 µL/mL did not induce transformation of BALB/3T3 cells; no metabolic activation was used in this assay.

Initiation and Promotion

No initiation or promotion studies were located for DUP.

Carcinogenicity Studies

No carcinogenicity studies were located for DUP.

6. EXPOSURE

Exposure to HMWPEs is believed to be primarily in the workplaces where manufactured. The primary workplace exposure in manufacturing activities would be dermal and may be potential for formation of aerosol during some applications (OECD, 2004). Because HMWPEs are handled only in industrial manufacturing facilities, minimal consumer exposure is expected

(OECD, 2004). The consumer is exposed indirectly through use of the products that may contain the HMWPEs and uptake is expected to be low (OECD, 2004). Exposure data specific to DUP were not found.

7. DISCUSSION

Appendix A provides a summary of the NOAELs and LOAELs for organ-specific endpoints for oral exposure to DUP. Studies for which effect levels for DUP were derived are limited to the 3-week dietary exposure study in rats (Barber et al., 1987; Chemical Manufacturers Association, 1985) and the 4-week gavage study in rats (Kwack et al., 2009). The dietary study examined a wide range of endpoints including the liver, a known target for phthalates, and defined NOAELs of 285/279 mg/kg-day and LOAELs of 1,183/1,106 mg/kg-day for males and females, respectively, for changes in liver weight and microscopic lesions. Body weight was also decreased at the same dose levels. The gavage study tested only a single dose level and did not include examination for pathology, but found an increase in the relative liver weight (18%) and serum chemistry changes indicative of liver toxicity at the tested dose of 500 mg/kg-day. This study also found that DUP decreased testicular weight (13%), and affected sperm count and motility at the same dose level. There is considerable uncertainty in these NOAEL and LOAEL values due to limitations in study design, including short exposure duration (3–4 weeks), small group sizes (five or six rats per group), and for the gavage study, limited investigation of endpoints (e.g., no liver pathology) and inclusion of only a single dose level, precluding illumination of the dose-response for the observed effects.

The database for the chemical is further limited by absence of studies of reproductive function and developmental toxicity. The effect on sperm observed in the gavage study is suggestive of an effect on male reproduction, but more detailed studies of generational exposure would be needed to make a definitive determination. The absence of developmental toxicity studies is an important data gap in light of the known effects of other phthalates on estrogen and androgen receptors, which modulate the development of reproductive organs.

8. REFERENCES

Barber ED, Still BD, Moran EJ, et al. (1987) Peroxisome induction on seven phthalate esters. Toxicol Ind Health 3:7–24.

Barber ED, Cifone M, Rundell J, et al. (2000) Results of the L5178Y mouse lymphoma assay and the Balb/3T3 cell *in vitro* transformation assay for eight phthalate esters. J Appl Toxicol 20:69–80.

Birch MD. (1951) Unpublished work, Younger Laboratories, Inc. and Monsanto. (Cited in Krauskopf, 1973).

Chemical Manufacturers Association. (1985) 21-day feeding study of diundecyl phthalate to rats: effects on the liver and liver lipids project No. 3.0495.4. Submitted under TSCA Section 4A. EPA Document No. 408526195. NTIS No. OTS0508502.

David, RM; McKee, RH; Butala, JH; et al. (2001) Esters of aromatic mono-,di-and tricarboxylic acids, aromatic diacids and di, tri, or polyalcohols. In: Bingham, B; Cohrssen; Powell, CH, eds. Patty's toxicology. 5th edition.New York, NY: John Wiley and Sons. Available online at http://onlinelibrary.wiley.com/book/10.1002/0471125474 (accessed May 9, 2011).

E.I. DuPont Denemours & Co. Inc. (1974) Skin irritation test on rabbits. Submitted under TSCA Section 8D. EPA Document No. 878221329. NTIS No. OTS0215201.

ECB (European Chemicals Bureau). (2000) Substance ID: 3648-20-2. Diundecyl phthalate. IUCLID Dataset. European Chemicals Bureau. European Commission. Available online at http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat (accessed October 12, 2010).

ExxonMobil. (2001) Plasticizers: Jayflex™ L11P-E plasticizer: Diundecyl Phthalate. http://www.exxonmobilchemical.com/Chem-English/Files/Resources/OXO_Jayflex_L11P-E_NA_en-FPS.pdf

HSDB (Hazardous Substance Data Bank). (2009) Diundecyl phthalate. National Library of Medicine HSDB Database. (Last Revision, 01/05/2009).

Krauskopf LG. (1973) Studies on the toxicity of phthalates via ingestion. Environ Health Perspect 3: 61–72.

Kwack SJ, Kim KB, Kim HS, et al. (2009) Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. J Toxicol Environ Health A 72:1446–1454.

Lawrence, WH; Turner, JE; Autian, J. (1971) Toxicity of ethylene chlorohydrin I: acute toxicity studies. J Pharm Sci 60:568–571.

Lawrence WH, Malik M, Turner JE, et al. (1975) A toxicological investigation of some acute, short-term, and chronic effects of administering di-2-ethylhexyl phthalate (DEHP) and other phthalate esters. Environ Res 9:1–11.

Medeiros AM, Devlin DJ, Keller LH. (1999) Evaluation of skin sensitization response of dialkyl (C_6–C_{13}) phthalate esters. Contact Dermatitis 41:287–289.

Monsanto. (1982) Material Safety Data Sheet, No. 364, January 8, 1982, St. Louis, MO, USA. (Cited in NICNAS, 2008).

NICNAS (National Industrial Chemicals Notification and Assessment Scheme). (2008) Diundecyl phthalate. Existing chemical hazard assessment report. National Industrial Chemicals Notification and Assessment Scheme. Australian government. Available online at http://www.nicnas.gov.au/Publications/CAR/Other/DUP%20hazard%20assessment.pdf (accessed October 13, 2010).

OECD (Organisation for Economic Cooperation and Development). (2004) SIDS initial assessment report for SIAM 19: Category high molecular weight phthalate esters. October 2004.

U.S. EPA. (2010) Hazard characterization document: screening-level hazard characterization, phthalate esters. U.S Environmental Protection Agency, April 2010.

Zeiger E, Haworth S, Mortelmans K, et al. (1985) Mutagenicity testing of di(2-ethylhexyl) phthalate and related chemicals in *Salmonella*. Environ Mut 7:213–232.

Appendix A. Summary of Endpoints by Organ System

Table A.1. Summary of NOAELs/LOAELs Identified for DUP by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
Fischer 344 rat (M&F)	Diet	0, 0.3, 1.2, or 2.5% (M: 0, 285, 1,183, or 2,495 mg/kg-day; F: 0, 279, 1,106, or 2,115 mg/kg-day) (5/sex/dose)	21 days	General	NOAEL=279–285 mg/kg-day LOAEL=1,106–1,183 mg/kg-day	Decreased body weight in both sexes	Barber et al., 1987; Chemical Manufacturers Association, 1985
				Hepatic	NOAEL=279–285 mg/kg-day LOAEL=1,106–1,183 mg/kg-day	Increased absolute and relative liver weight in both sexes; increased incidence of liver lesions (slight necrosis, vacuolation) in males	
Sprague-Dawley rat (M)	Oral gavage in corn oil	0 or 500 mg/kg-day (6/dose)	4 weeks	General	NOAEL=500 mg/kg-day LOAEL=None	No mortality and no effect on body weight	Kwack et al., 2009
				Hepatic	NOAEL=None LOAEL=500 mg/kg-day	Increased liver weight (18%) and serum AST and ALP	
				Reproduction	NOAEL=None LOAEL=500 mg/kg-day	Reduced testis weight (13%), sperm count, and motility	

Appendix B. Critical Study Reviews

Barber et al. (1987); Chemical Manufacturers Association (1985)

The ability of DUP to induce liver peroxisomes and related effects in rats was investigated in a 3-week feeding study (Barber et al., 1987; Chemical Manufacturers Association, 1985). DUP was fed to groups of five male and five female Fischer 344 rats at nominal dietary concentrations of 0, 0.3, 1.2, or 2.5% for 21 days. Although Chemical Manufacturers Association (1985) indicated that gas-liquid chromatography (GLC) of the test material showed it to be 48% DUP and 52% DUP isomers, Barber et al. (1987) stated that GLC analysis could not be conducted for DUP because the compound was a complex mixture and gave many peaks when assayed by GLC. Measured DUP concentrations throughout the study were within 5% of the nominal values. Reported average DUP intakes in the low-, mid- and high-dose male/female rats were 285/279, 1,183/1,106 and 2,495/2,115 mg/kg-day, respectively. General behavior and condition, body weight, and food consumption were assessed throughout the study. Endpoints evaluated at the end of the exposure period included serum triglyceride and total cholesterol levels, gross pathology of thoracic and abdominal viscera, and organ weight and histology of liver, kidney, and testis. The liver also was evaluated histochemically for presence and extent of neutral fat, examined by electron microscopy for peroxisome proliferation (two rats/sex in the control and the high-dose groups), and biochemically assayed (homogenates of remaining liver) for cyanide-insensitive palmitoyl-CoA oxidation, microsomal lauric acid 11- and 12-hydroxylases, and total and microsomal protein levels.

The rats were generally healthy during the study with no treatment-related behavioral variations or clinical signs. Body weight gain was slightly reduced in high-dose males and mid- and high-dose females, with no significant changes in food intake in either sex. Mean body weight was statistically significantly ($p < 0.05$) lower than controls in high-dose males and in mid- and high-dose females from day 7 on; differences with controls were >10% only in high-dose males during the latter portion of the study (13–15%). Although not statistically significant, a decrease in body weight was also seen in mid-dose males (approximately 5% at study termination; see Table B.1). Serum triglycerides were significantly reduced ($p < 0.001$) in mid- and high-dose males (approximately 52% in both groups) and so was cholesterol (33% in mid-dose males, $p < 0.01$; 35% in high-dose males, $p < 0.001$). No significant serum chemistry effects were observed in females. Significant changes in organ weights were restricted to mid- and high-dose rats (Table B.1). Both absolute and relative liver weights were increased in mid- (24 and 23%) and high-dose males (14 and 25%) and in mid- (33 and 34%) and high-dose

females (50 and 63%). Weight changes in other organs (testis, kidney) were consistent with decreased body weight in the mid- and high-dose groups (testis: increased relative weight with no change in absolute weight; kidneys: decreased absolute weight with no change in relative weight in males and increased relative weight with no change in absolute weight in females). Gross abnormalities were observed in the liver of mid- and high-dose rats, but not in any other organs; changes included pale and/or thickened liver in 3/5 mid-dose males and 2/5 high-dose males, and enlarged and/or darkened liver in 1/5 mid-dose females and 1/5 high-dose females. Significant histological effects occurred only in the liver; there were no treatment-related histological abnormalities in the kidney or testis.

Table B.1. Significant Changes in Body and Organ Weights at Necropsy in Fischer 344 Rats Exposed to DUP in the Diet for 21 Days

Dose (mg/kg-day)	Body Weight (g)	Liver		Kidney		Testis	
		Absolute (g)	Relative (g/100g Body Weight)	Absolute (g)	Relative (g/100g Body Weight)	Absolute (g)	Relative (g/100g Body Weight)
Males							
0	222 ± 4.5[a]	7.24 ± 0.22	3.26 ± 0.10	1.50 ± 0.04	0.68 ± 0.01	2.60 ± 0.07	1.17±0.03
285	224 ± 5.6	8.05 ± 0.41	3.59 ± 0.10	1.50 ± 0.06	0.67 ± 0.02	2.67 ± 0.05	1.20±0.02
1,183	211 ± 3.1	8.94 ± 0.40[b]	4.24 ± 0.18[b]	1.34 ± 0.03[b]	0.64 ± 0.01	2.65 ± 0.05	1.26±0.02[b]
2,495	194 ± 4.5[b]	8.42 ± 0.35[b]	4.34 ± 0.09[b]	1.29 ± 0.03[b]	0.67 ± 0.01	2.66 ± 0.05	1.38±0.03[b]
Females							
0	144 ± 1.5	4.36 ± 0.07	3.02 ± 0.06	1.03 ± 0.01	0.71 ± 0.01	–	
279	141 ± 3.4	4.48 ± 0.11	3.18 ± 0.06	0.99 ± 0.02	0.71 ± 0.02	–	
1,106	134 ± 1.3[b]	5.80 ± 0.24[b]	4.32 ± 0.15[b]	1.03 ± 0.04	0.77 ± 0.02[b]	–	
2,115	133 ± 2.4[b]	6.53 ± 0.36[b]	4.92 ± 0.23[b]	1.04 ± 0.02	0.79 ± 0.01[b]	–	

[a]Mean ± SE for groups of five rats.
[b]$p < 0.05$.
Source: Chemical Manufacturers Association (1985).

Table B.2 shows the results of histological examination of the liver. The incidences of liver lesions (slight necrosis, slight/moderate vacuolation) were significantly increased in mid- and high-dose males. The degree of cytoplasmic basophilia was decreased in mid- and high-dose males and females. The researchers considered this change in cytoplasm staining characteristics to likely reflect a change in the organelle component and metabolic status of the cell, and noted that similar changes produced by other compounds were associated with increases in smooth endoplasmic reticulum and associated structures. Ultrastructural examination of the liver confirmed that there was a marked increase in fatty vacuolation and distension of smooth

and rough endoplasmic reticulum in high-dose males and revealed an overall moderate proliferation of peroxisomes in the periportal and centrilobular areas in high-dose males and females; low- and mid-dose rats were not examined. Biochemical analyses showed increases in liver enzymes and total hepatic protein, consistent with peroxisome stimulation. Cyanide-insensitive palmitoyl-CoA oxidation levels had dose-related increases in both sexes that were statistically significant ($p < 0.001$) in mid- and high-dose males and females. Lauric acid 11- and 12-hydroxylase activities were significantly increased ($p < 0.01$) in males at all dose levels and in high-dose females. Total hepatic protein concentrations were significantly increased ($p < 0.01$) in mid- and high-dose females, but there were no significant changes in total hepatic protein in males or microsomal protein level in either sex.

Table B.2. Incidence of Histological Liver Changes in Fischer 344 Rats Exposed to DUP in the Diet for 21 Days

	Males				Females			
Dose (mg/kg-day)	**0**	**285**	**1,183**	**2,495**	**0**	**279**	**1,106**	**2,115**
Reduced cytoplasmic basophilia	0/5	0/5	5/5[a]	5/5[a]	0/5	0/5	4/5[a]	5/5[a]
Slight increase individual cell necrosis	0/5	0/5	4/5[a]	5/5[a]	0/5	0/5	0/5	0/5
Slight cell vacuolization	0/5	0/5	2/5	4/5[a]	1/5	0/5	0/5	0/5
Moderate cell vacuolization	0/5	0/5	5/5[a]	3/5	0/5	0/5	0/5	0/5

[a] $p < 0.05$ (Fisher's exact test conducted by for this review).
Source: Chemical Manufacturers Association (1985).

A NOAEL of 0.3% (285 and 279 mg/kg-day in males and females, respectively) and a LOAEL of 1.3% (1,183 and 1,106 mg/kg-day, respectively) are identified for rats in this study based on decreased body weight and increased absolute and relative liver weight in both sexes, and increased incidence of liver lesions in males.

Kwack et al. (2009)

In a more recent study, groups of male Sprague-Dawley rats (6/group) were administered 0 (vehicle control) or 500 mg DUP/kg-day by gavage in corn oil for 4 weeks (Kwack et al., 2009). All rats were observed after administration of the test material for possible signs of toxicity. Body weight was monitored repeatedly throughout the study. Food consumption was measured at the beginning of the study and twice/week during the last week of treatment. Before

termination, urine was collected for 12 hours for urinalysis. At termination, the heart, lung, liver, kidneys, adrenal glands, spleen, thymus, thyroid glands, testes, and epididymides were weighed for determination of relative organ weights. Blood was collected at this time for comprehensive hematological and clinical chemistry testing (including electrolytes). The right cauda epididymis was used for sperm count analysis and the left was used for motility analysis. Specific motility parameters measured included percentage of motile sperm, average path velocity, straight-line velocity, curvilinear velocity, amplitude of the lateral head displacement, beat cross frequency, straightness, and linearity. No examination for organ pathology was performed for this study.

There was no mortality during the study. Clinical signs were limited to salivation immediately after dosing. Neither food consumption nor body weight was significantly altered by treatment with DUP. Most relative organ weights and hematological parameters were also not affected by dosing with DUP. Relative liver weight was increased eighteen percent, but this difference was not statistically significant. Serum chemistry analyses showed significant increases in total protein (9.1% over control), AST (50% over control), and ALP (81% over control). Results of the urinalyses were unremarkable. The relative testis weight was decreased thirteen percent, but this difference was not statistically significant. Treatment with DUP significantly reduced both sperm count (28%) and motility (63%). Specific motility parameters significantly reduced were curvilinear velocity (17%), straightness (19%), and linearity (19%).

Based on the changes in relative liver weight and serum chemistry endpoints suggestive of a toxic effect on the liver (increased AST and ALP) and the reductions in testis weight, sperm count and motility, the dose of 500 mg/kg-day is a LOAEL, but it cannot be considered a reliable LOAEL because only one dose level (with only 5-6 rats per dose) was used; the true LOAEL may be lower.