UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
Bethesda, MD 20814

Memorandum

Date: October 30, 2010

TO : Michael A. Babich, Ph.D., Project Manager, Phthalates, Section 108 of CPSIA

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences
Lori E. Saltzman, M.S., Director, Division of Health Sciences

FROM : Kent R. Carlson, Ph.D., Toxicologist, Directorate for Health Sciences
Leslie E. Patton, Ph.D., Toxicologist, Directorate for Health Sciences

SUBJECT : Toxicity Review of **Di(2-propylheptyl) phthalate (DPHP)**

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 **DPHP**.

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

* This report was prepared for the Commission pursuant to contract CPSC-D-06-0006. It has not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

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 DI(2-PROPYLHEPTYL) PHTHALATE

Contract No. CPSC-D-06-0006
Task Order 012

Prepared by:

Versar Inc.
6850 Versar Center
Springfield, VA 22151

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

Prepared for:

Kent R. Carlson, Ph.D.
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

May 16, 2011

TABLE OF CONTENTS

TOXICITY REVIEW FOR DI(2-PROPYLHEPTYL) PHTHALATE (DPHP)

TABLE OF CONTENTS (Continued)

LIST OF TABLES

LIST OF ABBREVIATIONS AND ACRONYMS

DPHP	Di(2-propylheptyl) phthalate
GD	Gestation day
NOAEL	No-observed-adverse-effect level
LOAEL	Lowest-observed-adverse-effect level
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose

EXECUTIVE SUMMARY

DPHP is a high production volume plasticizer found in a variety of consumer products.

Exposure to DPHP resulted in an oral LD_{50} > 5,000 mg/kg in one rat study. In a dermal exposure study, administration of DPHP resulted in an LD_{50} > 2,000 mg/kg in rabbits. One hour inhalation exposures resulted in an LC_{50} > 20.5 mg/L in rats. In two rabbit studies, dermal exposure to DPHP resulted in no to slight irritation of the skin. In an additional study, dermal exposure to guinea pigs caused minimal erythema. Ocular exposure to DPHP did not cause eye irritation in one rabbit study and only slight irritation in another rabbit study. No dermal sensitization was seen in guinea pigs following challenge applications of DPHP.

Evidence supported the conclusion that DPHP was a subchronic toxicant. Exposure to DPHP induced significant decrements in male and female body weight and food consumption. Although not verified by additional studies, significant changes in adrenal and liver histopathology, blood composition, and increased incidence in soft tissue variations (dilated renal pelvis) and reproductive parameters (which may be related to maternal toxicity) also supported the conclusion that DPHP was a subchronic toxicant.

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 DPHP relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data 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.

Even though there is evidence to support the conclusion that DPHP has subchronic toxicity, the lack of supporting studies and paucity of methodological details suggests that there was “inadequate evidence” for the designation of DPHP as a “chronic hazard” when considering FHSA criteria (16 CFR §1500.135).

TOXICITY REVIEW FOR DI(2-PROPYLHEPTYL) PHTHALATE
(DPHP, CASRN 53306-54-0)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with di(2-propylheptyl) phthalate (DPHP). This assessment was prepared from a variety of review articles (NICNAS, 2003; RIVM, 2006) 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

DPHP is an *ortho* phthalate with a backbone of C7 branched with a propyl side chain. DPHP is currently considered to belong to the High Molecular Weight Phthalate Esters (HWMPE) group. DPHP is a specific isomer of di-isodecyl phthalate (DIDP) (NICNAS, 2003). The identity and physicochemical properties of DPHP can be seen in Tables 2.1 and 2.2 (NICNAS, 2003).

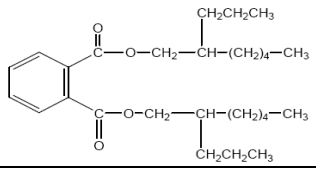
Table 2.1 Names, Structural Descriptors, and Molecular Formulas of DPHP (NICNAS, 2003)	
CAS Number:	53306-54-0
Chemical Name:	1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester
Common Name	di(2-propylheptyl) phthalate (DPHP)
Molecular Formula:	C28H46O4
Structural Formula:	
Molecular Weight:	446.68
Synonyms:	Bis(2-propylheptyl) phthalate; Di-2-propylheptyl phthalate; phthalic acid, bis(2-propylheptyl) phthalate; phthalic acid, bis(2-propylheptyl) ester
Purity/Impurities/Additives:	Purity: >99.5% w/w; Impurity: 1,2-Benzenedicarboxylic acid, bis(4-methyl-2-propylhexyl) ester (weight % = 2); Impurity: 1,2-Benzenedicarboxylic acid, 4-methyl-2-propylhexyl 2-propylheptyl ester (weight % =15); Stabilizer: 0.1% Topanol CA; 0.3-0.5% bisphenol A (4,4'-isopropylidenediphenol)

Table 2.2 Physicochemical Properties of DPHP (NCINAS, 2003; RIVM, 2006)	
Property	**Value**
Physical state	Clear, oily, mobile liquid with a faint odor (20ºC and 101.3 kPa) (NCINAS, 2003)
Melting point	-48ºC (RIVM, 2006)
Boiling point	254ºC (RIVM, 2006)
Density	960-968 kg/m^3 (NICNAS, 2003)
Vapor pressure	3.7 x 10^{-9} kPa (20°C) (NICNAS, 2003); 3.7 x 10^{-6} Pa (RIVM, 2006)
Water solubility	1 x 10^{-4} mg/L (RIVM, 2006); ~ 0.2 µg/L (NCINAS, 2003)
Partition coefficient n-octanol/water (log Kow)	>6 (NICNAS, 2003)
Henry's law constant	Not reported
Flash point	~ 238ºC (NICNAS, 2003)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

In general, DPHP is manufactured commercially in a closed system by catalytically esterifying phthalic anhydride with isomeric decyl alcohols (primarily 2-propyl heptanol). As with other phthalates, the unreacted alcohols are recovered and reused, and the DPHP mixture is purified by vacuum distillation or activated charcoal. The purity of DPHP can achieve 99% or greater using current manufacturing processes. Bisphenol A (0.3-0.5%) and Topanol CA (0.1%) may be added as stabilizers. The remaining fraction of DPHP may contain a maximum of 0.1% water. Impurities in DPHP may include 1,2-Benzenedicarboxylic acid, bis(4-methyl-2-propylhexyl) ester and 1,2-Benzenedicarboxylic acid, 4-methyl-2-propylhexyl 2-propylheptyl ester.

BASF manufactures Palatinol® DPHP (Texas), Palatinol® DPHP-E (stabilized with 0.3% bisphenol-A; Texas), Palatinol® DPHP-I (stabilized with 0.1% Topanol CA; Texas), Palatinol® 10-P (Germany), and Palatinol® 10-P stab (stabilized with 0.5% bisphenol A; Germany). These products have stated applications as low fog artificial leather (automobiles) and wire and cable applications (for wires rated to 80ºC). BASF also produces a blended product with enhanced weatherability and cold flexibility (Palatinol® 1086; Texas) consisting of 85% Palatinol® DPHP and 15% Plastomoll DOA [di-(2-ethylhexyl) adipate]. Perstorp Oxo AB also manufactures DPHP under the trade name Emoltene™ 100 (Sweden).

Supply

U.S. production of DPHP has been reported as 105,000 metric tons (2008) and is projected to increase to 119,000 metric tons (2013). DPHP's proportion of the total phthalate production market (18.0%) is also projected to increase (to 21.2%) during the same period (+2.5% growth rate; Bizzari et al. 2009). This is a remarkable increase from 2005 estimated production and proportion of the market figures (negligible production, <0.5% of phthalate production market; Bizzari et al. 2007).

U.S. consumption of DPHP has been reported as 86,000 metric tons (2008) and is projected to increase to 96,000 metric tons (2013). DPHP's proportion of the total phthalate consumption market (14.3%) is also projected to increase (to 16.4%) during the same period (+2.2% growth rate; Bizzari et al. 2009). This is a remarkable increase from 2005 estimated consumption and proportion of the market figures (5,000 metric tons, 0.8% of phthalate

consumption market; Bizzari et al. 2007). Western European consumption has followed a similar pattern from neglible consumption in 2002 to 55,000 metric tons in 2008. Consumption is expected to top 120,000 metric tons in 2013.

In 2008, U.S. consumption (in metric tons) of DPHP was approximately 19,000 metric tons lower than production estimates. This suggests that most linear C9-C11 phthalates produced in the U.S. are utilized locally and also that a moderate amount of DPHP may be exported.

Currently, BASF is the major U.S. producer of DPHP. It has recently commissioned (2007) a plant in Pasadena Texas to produce DPHP. The plant has a maximum capacity of 125,000 metric tons (Bizzari et al. 2009).

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 and compressor fluids (NICNAS, 2008).

DPHP is used as a plasticizer for PVC and vinyl chloride copolymers and has replaced some linear phthalates (DIDP, DINP). End-use products containing DPHP include automobile undercoating, building materials, tarpaulins, wires, cables, shoes, component of sealants and adhesives, in rubber articles, in food container gaskets, carpet backing, pool liners and gloves (NICNAS, 2003). The U.S. FDA has also approved DPHP for use in food packaging and handling. Typical concentrations of DPHP in end-use products range from 30 to 60 percent (NICNAS, 2003).

4. TOXICOKINETICS

Wittassek and Angerer (2008) reported that 61 hours after oral administration of an unspecified dose of DPHP to a healthy male volunteer, the subject excreted approximately 34% of the dose in the urine, mainly as hydroxy (OH-MPHP; ~ 17%) and oxo metabolites (oxo-MPHP; ~ 16%), with a lesser amount as carboxy metabolites (cx-MPHP; < 5%). The simple monoester in the urine (MPHP) accounted for <1% of the administered dose. No further relevant information was located.

5. HAZARD INFORMATION

This section contains brief hazard summaries of the adverse effects of DPHP in a variety of animal species. 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 DPHP resulted in an oral LD_{50} > 5,000 mg/kg in one rat study. In a dermal exposure study, administration of DPHP resulted in an LD_{50} > 2,000 mg/kg in rabbits. One hour inhalation exposures resulted in an LC_{50} > 20.5 mg/L in rats. In two rabbit studies, dermal exposure to DPHP resulted in no to slight irritation of the skin. In an additional study, dermal exposure to guinea pigs caused minimal erythema. Ocular exposure to DPHP did not cause eye irritation in one rabbit study and only slight irritation in another rabbit study. No dermal sensitization was seen in guinea pigs following challenge applications of DPHP.

Evidence supported the conclusion that DPHP was a subchronic toxicant. Exposure to DPHP induced significant decrements in male and female body weight and food consumption. Although not verified by additional studies, significant changes in adrenal and liver histopathology, blood composition, and increased incidence in soft tissue variations (dilated renal pelvis) and reproductive parameters (which may be related to maternal toxicity) also support the conclusion that DPHP is a subchronic toxicant.

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 DPHP relevant exposure durations for the

general population or for other sensitive subpopulations because confirmatory data 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

No deaths were reported in a group of five male and five female Sherman-Wistar rats treated with a single gavage dose of 5,000 mg/kg of DPHP (91.3% pure; 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl phthalate) and observed for 14 days, indicating an oral LD_{50} of >5,000 mg/kg (Nuodex, Inc., 1979a). No unusual behavioral signs were noted and gross necropsy of the rats was unremarkable. No other relevant studies were located.

Sufficient detail was provided in this study to consider it acceptable for use. The estimated LD_{50} from the Nuodex (1979a) study is higher than the oral LD_{50} range (50 to 5,000 mg/kg) required by the FHSA to conclude that a chemical is acutely toxic. The weight of evidence including probable animal data are sufficient, therefore, to support the conclusion that DPHP does not fit the definition of "acutely toxic" via oral exposure under the FHSA (16 CFR §1500.3(c)(2)(i)(A)).

5.2. Acute Dermal Toxicity

A dermal LD_{50} >2,000 mg/kg was reported based on an experiment in which a group of three male and three female albino rabbits had 2,000 mg DPHP/kg (91.3% pure; 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl phthalate) applied to a clipped

and abraded area of the back for 24 hours (Nuodex, Inc., 1979b). The application site was covered, and excess material was removed after the 24-hour exposure period. No clinical signs were noted during the 14-day observation period, and no animals died during this time. Gross necropsy was unremarkable. No other relevant studies were located.

Sufficient detail was provided in this study to consider it acceptable for use. The estimated LD_{50} from the Nuodex (1979b) study is higher than the dermal LD_{50} range (200 to 2,000 mg/kg) required by the FHSA to conclude that a chemical is acutely toxic. The weight of evidence including probable animal data are sufficient, therefore, to support the conclusion that DPHP does not fit the definition of "acutely toxic" via dermal exposure under the FHSA (16 CFR §1500.3(c)(2)(i)(C)).

5.3. Acute Inhalation Toxicity

A group of five male and five female albino rats (strain not specified) was exposed whole-body to 20.5 mg/L (the maximum concentration that could be attained) of DPHP (91.3% pure; 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl phthalate) as an aerosol (particle diameter = 3–5 microns) for 1 hour and observed for 14 days (Nuodex, Inc., 1979c). The rats were wet, ruffled, agitated, and raspy sounding immediately after exposure, but appeared normal 24 hours after exposure. No rats died during the study and gross necropsy did not reveal significant alterations. This study suggests a 1-hour LC_{50} of >20.5 mg/L in rats. No other relevant studies were located. Calculations estimate a 4h LC_{50} of > 5 mg/L.

Sufficient detail was provided in this study to consider it acceptable for use. The estimated LD_{50} from the Nuodex (1979c) study is higher than the inhalation LD_{50} value (2 mg/L) required by the FHSA to conclude that a chemical is "highly toxic". The weight of evidence including probable animal data are sufficient, therefore, to support the conclusion that DPHP does not fit the definition of "highly toxic" via inhalation under the FHSA (16 CFR §1500.3(b)(6)(i)(B)). The lack of additional acute inhalation toxicity data for DPHP can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of DPHP as "acutely toxic" (< 200 mg/L) via inhalation under the FHSA (16 CFR §1500.3(c)(2)(i)(B)).

5.4. Primary Skin Irritation

Nuodex, Inc. (1979d) reported that application of 0.5 g of DPHP (91.3% pure) to intact or abraded areas on the clipped back of six albino rabbits (strain not specified) under occlusion for 24 hours did not cause irritation. Observations were conducted at 24 and 72 hours. None of animals showed any evidence of erythema or edema at either time point. In another study, application of an unspecified amount of DPHP to the skin of New Zealand White rabbits (one male and two females) under "semi-occlusive" conditions caused slight irritation, based on scores recorded at 24, 48, and 72 hours; a Primary Irritation Index of 0.25 was reported (BASF, 2002a, as cited in NICNAS, 2003). In guinea pigs (five per sex) given 10 repeated 24-hour applications of 500 mg of DPHP (91.3% pure) to intact skin under occlusion at 48-hour intervals, several of the animals tested showed evidence of minimal erythema following applications 5–10 (Nuodex, Inc., 1979e).

Slight dermal irritation was noted in a rabbit study and minimal erythema in a guinea pig study. One additional rabbit study did not report any dermal irritation following exposure. The estimated “scores” from the guinea pig and rabbit 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 animal data supported the conclusion that DPHP 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

Instillation of 100 mg DPHP (91.3% pure) into the right eyes of six albino rabbits (the left eyes served as untreated controls) produced no evidence of ocular irritation, based on examinations of the cornea, iris, and conjunctiva of the unwashed eyes at 1, 24, 48, and 72 hours, and 5 and 7 days after instillation of the chemical (Nuodex, Inc., 1979f). In another study, DPHP was slightly irritating to the eye of New Zealand White rabbits, producing redness in the conjunctiva of the three tested rabbits in observations recorded at 24, 48 and 72 hours (BASF, 2002b, as cited in NICNAS, 2003).

The lack of additional information and the presence of conflicting data on the ocular properties of DPHP can be considered a data gap and supports the conclusion that there is “inadequate evidence” for the designation of DPHP as a “primary ocular irritant” under the FHSA (16 CFR §1500.3(c)(3). Weight of the animal evidence does support the conclusion,

however, that DPHP did not fit the definition of "corrosive" to the eyes under the FHSA (16 CFR §1500.3(c)(4)).

5.6. Sensitization

DPHP was tested for skin sensitization in guinea pigs. In the Nuodex, Inc. (1979e) repeated dermal application study described above, the 10th application was followed by a 2-week rest period. At that time, 24-hour challenge applications were placed at skin sites different from the original sites. The challenge sites were examined for evidence of irritation after 24 and 48 hours. There was no evidence of erythema or edema at either time point in the challenge test.

A sufficient weight of animal evidence suggests that DPHP 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)

Limited information exists regarding the repeated-dose systemic toxicity of DPHP. Union Carbide Corporation (1998, 1997) provided a brief summary of preliminary findings of a 90-day dietary study in rats. Groups of Alpk:APfSD rats (12/sex/group) were fed a diet containing 0, 500, 5,000, or 12,000 ppm DPHP for 90 days. Without providing details, the summary states that these concentrations provided doses of approximately 0, 40, 420, and 1,000 mg DPHP/kg-day. Animals were sacrificed at termination of exposure, and organs and tissues were collected and processed for microscopic examination. In addition, blood samples were taken and subjected to standard hematological and clinical chemistry tests. The study also included two recovery groups that were fed 0 or 12,000 ppm in the diet for 90 days and then held for 4 weeks for observation before being sacrificed. Body weight gain was reported to be significantly decreased in the high-dose rats treated with 1,000 mg/kg-day, with body weight decreases (relative to controls) of 23 and 19% in males and females, respectively, at the end of the exposure period. The difference in body weight gain was reportedly partially resolved following the 4-week recovery period. The reduced weight gain in the 1,000 mg/kg-day group was accompanied by a decrease in food consumption, the magnitude of which was not specified. A smaller body weight reduction of 6% was reported in males of the 420 mg/kg-day group. The data were not shown and no further details were provided in the available reports.

In a different study, groups of presumed pregnant female Wistar rats (25/group) were administered 0, 40, 200, or 1,000 mg DPHP/kg-day by gavage (vehicle not specified) on gestation days (GDs) 6 through 19 (BASF, 2003). Maternal toxicity occurred in the high-dose group (1,000 mg/kg-day), as evidenced by insufficient care of fur, 32% reduced food consumption on GDs 6–10, and 30% reduced corrected body weight gain. Significant loss of body weight (magnitude not specified) occurred on GDs 6–8.

5.8. Hematological Effects

Blood samples were collected and analyzed for standard hematological endpoints in the Union Carbide Corporation (1998, 1997) 90-day rat study of DPHP. Hematology findings in the rats consisted of reductions (of unspecified magnitude) in red blood cell count, hemoglobin, and hematocrit, and increased platelet counts in male rats at ≥420 mg/kg-day and female rats at 1,000 mg/kg-day. The data were not shown and no further details were provided in the available reports.

5.9. Hepatic Effects

Union Carbide Corporation (1998, 1997) provided a brief summary of preliminary findings of the 90-day dietary DPHP study in rats. According to the summary, increased liver weights with concurrent increases in peroxisome enzyme levels were seen in all treated groups (≥40 mg/kg-day), and histopathological lesions consistent with peroxisome proliferation (not further described) were seen in the livers of both males and females at ≥420 mg/kg-day. The researchers also reported increased activity (presumably in the liver) of cyanide insensitive palmitoyl CoA, an enzyme associated with peroxisome proliferation (it is not clear from the report whether this is the enzyme change referred to above), and decreased plasma cholesterol and triglyceride, other changes consistent with peroxisome proliferation, at unspecified dose levels. However, the data were not shown and no further details were provided in the available reports.

Overall, an insufficient amount of animal data and poorly described methodologies in studies using DPHP as a test substance supported the conclusion that there was “insufficient evidence” for the designation of DPHP as a “hepatotoxicant”.

5.10. Adrenal Effects

The Union Carbide Corporation (1998, 1997) study reported adrenal effects in rats treated with DPHP in the diet for 90 days. Histological examination of the adrenal gland revealed a characteristic vacuolization of the *zona glomerulosa* in both sexes and in all treatment groups (≥40 mg/kg-day). The severity of the lesion was dose-related; it was described as minimal in the 40 mg/kg-day group, slight in the 420 mg/kg-day group, and moderate in the 1,000 mg/kg-day group. Clinical chemistry tests showed decreased plasma sodium and increased plasma potassium in the 1,000 mg/kg-day males and females that the researchers considered to be potentially related to the adrenal changes. No data were shown and no further details were provided in the available reports of this study.

Overall, an insufficient amount of animal data and poorly described methodologies in studies using DPHP as a test substance supported the conclusion that there was "insufficient evidence" for the designation of DPHP as an "adrenal toxicant".

5.11. Reproductive Toxicity

The Union Carbide Corporation (1997) preliminary summary report stated that high-dose male rats (1,000 mg DPHP/kg-day) exposed to DPHP for 90 days in the diet showed statistically significant (12.5–25%) reductions in sperm velocity indices, which were not observed after the 4-week recovery period. Other indices of sperm viability, such as total sperm, static count, percent motile, motile count, total sperm concentration, and concentration of sperm per gram of tissue, were not significantly affected by 90 days of dosing with DPHP. The toxicological significance of the decrease in sperm velocity is unknown, particularly since all other sperm parameters were unaffected. Fertility was not assessed.

In a review of phthalate reproductive effects, Fabjan et al. (2006) reported that doses of 50, 250, or 1,500 mg DPHP/kg-day administered to rats via the diet for 3 months, a period sufficient to cover the complete sperm maturation, had no significant effect on the reproductive organs in rats. However, it was not indicated which reproductive organs were examined and how, or whether females were included in the study. No original reference for this study was cited in the review.

Overall, an insufficient amount of animal data and poorly described methodologies in studies using DPHP as a test substance supported the conclusion that there was "insufficient evidence" for the designation of DPHP as a "reproductive toxicant".

5.12. Prenatal, Perinatal, and Post-natal Toxicity

A gestational exposure study of DPHP in rats is available as a brief report of preliminary results (BASF, 2003). Groups of presumed pregnant female Wistar rats (25/group) were administered 0, 40, 200, or 1,000 mg DPHP/kg-day by gavage (vehicle not specified) on gestation days (GDs) 6 through 19. At necropsy (not specified but presumably GD 20), 17–25 females per group had implantation sites. Maternal toxicity occurred in the high-dose group (1,000 mg/kg-day), as evidenced by insufficient care of fur, 32% reduced food consumption on GDs 6–10, and 30% reduced corrected body weight gain. Significant loss of body weight (magnitude not specified) occurred on GDs 6–8. Gross necropsy showed that two high-dose females had hydrometra (accumulation of fluid in the uterus). Examination of the uterus showed that high-dose females had increased postimplantation loss compared with controls (21.3 vs. 6.2%). In addition, 17/20 high-dose females (it is unclear what happened with the remaining five females in this group) had viable fetuses, and in three dams, only resorptions were found in the uterus (2.2 vs. 0.5% in controls). Exposure to DPHP did not cause teratogenicity, but fetuses from high-dose females showed a statistically significant increased incidence in soft tissue variations (dilated renal pelvis), which according to the researchers, was just outside the historical control range. It should be noted that this study is also summarized in the review by Fabjan et al. (2006), which states that the rates of soft tissue, skeletal, and total variations were slightly but statistically significantly increased in high-dose fetuses. Fabjan et al. (2006) also reported a screening developmental toxicity study (citation not provided) in which pregnant rat dams were treated with DPHP on GDs 6–15 by gavage with no maternal or fetal effects at the high dose of 1,000 mg/kg-day. No data were shown and no further details were provided in the available reports of these studies.

Overall, an insufficient amount of animal data and poorly described methodologies in studies using DPHP as a test substance supported the conclusion that there was "insufficient evidence" for the designation of DPHP as a "developmental toxicant".

5.13. Carcinogenicity

Genotoxicity

No genotoxicity studies were located for DPHP.

Initiation and Promotion

No initiation or promotion studies were located for DPHP.

Carcinogenicity Studies

No carcinogenicity studies were located for DPHP.

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).

DPHP is used mainly for wire, cable and automotive parts (NCINAS, 2003). The general population may have limited dermal contact with wires and cables but more frequently have dermal contact with automotive parts containing DPHP (NICNAS, 2003). Because DPHP will not be chemically bound, it may be released from end-products over time such as volatilization from car upholstery (NCINAS, 2003). The general population, including children, may be potentially exposed (NCINAS, 2003).

Specific exposure data to DPHP were not found.

7. DISCUSSION

Overall Uncertainty

The hazard database for DPHP consisted primarily of a few poorly described "reproduction" and "developmental" studies. Additional studies satisfactorily described acute effects of single DPHP exposures.

Toxicity data associated with DPHP exposure are limited. No reliable no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) values for reproductive, developmental, or repeated-dose systemic toxicity were identified. Limitations of the available database include lack of quantitative information that could have helped discern NOAELs from LOAELs, few endpoints examined, and lack of evaluations of endocrine endpoints known to depend on the estrogen and androgen receptor, which are affected by other phthalates, such as di(2-ethyhexyl) phthalate.

Overall Acceptable Daily Intakes

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 DPHP relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data on toxicological endpoints and methodological clarifications were not available.

8. REFERENCES

BASF. (2002a) Palatinol 10-P, acute dermal irritation/corrosion in rabbits, BASF Germany (unpublished report, provided by the notifier) (cited in NICNAS, 2003).

BASF. (2002b) Palatinol 10-P, acute eye irritation in rabbits, BASF Germany (unpublished report, provided by the notifier) (cited in NICNAS, 2003).

BASF. (2003) Oral gavage prenatal developmental toxicity study in rats (OECD TG 414). Submitted under TSCA Section 8E; 8EHQ-1003-15438A.

Bizzari, S.N., Blagoev, M., and A. Kishi. (2007) CEH Marketing Research Report. Plasticizers. SRI Consulting. 148pp.

Bizzari, S.N., Blagoev, M., and A. Kishi. (2009) CEH Marketing Research Report. Plasticizers. SRI Consulting. 169pp.

Fabjan E, Hulzebos E, Mennes W, et al. (2006) A category approach for reproductive effects of phthalates. Crit Rev Toxicol 36:695–726.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme). (2003) 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester (Palatinol 10-P). Australian Government. STD/1054. Available online at http://www.nicnas.gov.au/publications/CAR/new/Std/stdFULLR/std1000FR/std1054FR.pdf (accessed October 15, 2010).

NICNAS (National Industrial Chemicals Notification and Assessment Scheme). (2008) Ditridecyl phthalate. Existing chemical hazard assessment report. Phthalates Hazard Compendium. Australian Government. Available online at http://www.nicnas.gov.au/Publications/CAR/Other/Phthalate%20Hazard%20Compendium.pdf (accessed April 30, 2011)

Nuodex, Inc. (1979a) Mixed C-10 alkyl phthalates. Submitted under TSCA Section 8d; EPA Document No. 878210227; NTIS No. OTS0206260.

Nuodex, Inc. (1979b) Acute dermal toxicity-rabbits. Submitted under TSCA Section 8D; EPA Document No. 878211988; NTIS No. OTS0206260.

Nuodex, Inc. (1979c) Acute inhalation toxicity-rats. Submitted under TSCA Section 8D; EPA Document No. 878211987; NTIS No. OTS0206260.

Nuodex, Inc. (1979d) Primary skin irritation study-rabbits. Submitted under TSCA Section 8D; EPA Document No. 878211990; NTIS No. OTS0206260.

Nuodex, Inc. (1979e) Guinea pig contact dermal irritation/sensitization. Submitted under TSCA Section 8D; EPA Document No. 878211986; NTIS No. OTS0206260.

Nuodex, Inc. (1979f) Primary eye irritation study-rabbits. Submitted under TSCA Section 8D; EPA Document No. 878211989; NTIS No. OTS0206260.

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

RIVM (National Institute for Public Health and the Environment). (2006)Workability of the guidance documents for the category or read-across approach for selected groups of chemicals. Ministry of Housing, Spatial Planning and the Environment of Netherlands. RIVM report 601200009/2006.

Union Carbide Corporation. (1997) Letter from Union Carbide Corp to USEPA regarding: bis-2-propylheptyl phthalate subchronic feeding study in rats, dated 03/17/1997. Submitted under TSCA Section FYI. EPA Document No. FYI-OTS-0397-1292. NTIS No. OTS0001292.

Union Carbide Corporation. (1998) Support letter from Union Carbide Corp to USEPA regarding 90-day rat feeding study with bis-2-propylheptyl phthalate, dated 01/15/1998. EPA Document No. FYI-OTS-0198-1292. NTIS No. OTS0001292.

Wittassek M, Angerer J. (2008) Phthalates: metabolism and exposure. Int J Androl 31:131–138.