UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
Bethesda, MD 20814

Memorandum

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SUBJECT : Toxicity Review of **Diisooctyl phthalate (DIOP)**

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 **DIOP**.

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 DIISOOCTYL PHTHALATE (DIOP)

Contract No. CPSC-D-06-0006
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LIST OF ABBREVIATIONS AND ACRONYMS

BBP	n-butyl benzyl phthalate
CDC	U.S. Centers for Disease Control and Prevention
DBP	Dibutyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DIOP	Diisooctyl phthalate
FDA	Food and Drug Administration
FHSA	Federal Hazardous Substances Act
HMWPE	High molecular weight phthalate ester
HSDB	Hazardous Substance Data Bank
LC-MS	Liquid chromatography-mass spectrometry
LOAEL	Lowest-observed-adverse-effect level
MBP	Mono-*n*-butyl phthalate
MCPP	Mono-(3-carboxypropyl) phthalate
MEHP	Mono-(2-ethylhexyl) phthalate
MiNP	Mono-(3-methyl-5-dimethylhexyl) phthalate
MiDP	Mono-(3-methyl-7-methyloctyl) phthalate
MnOP	Mono-*n*-octyl phthalate
NICNAS	Australian National Industrial Chemicals Notification and Assessmnt Scheme
NOAEL	No-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PVC	Polyvinyl chloride

EXECUTIVE SUMMARY

DIOP is a minor use plasticizer found in a variety of consumer products.

Exposure to DIOP resulted in an oral LD_{50} = 2769 mg/kg in one mouse study, and >22,000 mg/kg in two other studies (rat and mouse). Dermal toxicity with LD50s > 3160 mg/kg were reported in two rabbit studies. DIOP was a severe dermal irritant at high doses in one well conducted rabbit study, but only a minimal to mild irritant in two other studies (rabbit and rat). There was inadequate evidence to determine if DIOP was an acute inhalation toxicant, a primary ocular irritant, a sensitizer, or a chronic toxicant. Studies provided were also inadequate to determine if DIOP was a carcinogen, reproductive toxicant, or developmental toxicant.

In summary, data supports the conclusion that DIOP can be considered a "primary dermal irritant" under the FHSA due to the generation of dermal erythema following short-term high-concentration exposures.

TOXICITY REVIEW FOR DIISOOCTYL PHTHALATE (DIOP, CASRN 27554-26-3)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with diisooctyl phthalate (DIOP). This assessment was prepared from a variety of review articles (NICNAS, 2008; U.S. EPA, 2010; ECB, 2000, 2008) 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 DIOP.

DIOP is comprised of a pair of seven-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*).

DIOP has at least two isomers [di(1-methylheptyl) phthalate, CAS RN 3198-29-6; and bis(6-methylheptyl) phthalate, CAS RN 1330-91-2], and is usually present as a mixture comprising 70-75% C4-C6 and less than 25% phthalate esters with chain lengths of C7 or more(ACC, 2001).

Controversy exists regarding the classification of DIOP. DIOP is considered to belong to the High Molecular Weight Phthalate Esters (HMWPE) group by the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2008) and EPA (U.S. EPA, 2010). It is considered a transitional phthalate, however, by the European Chemicals Bureau (ECB; IUCLID, 2007) and the American Chemistry Council Phthalate Esters Panel HPV Testing Group (ACC 2001).

The identity and physicochemical properties of DIOP can be seen in Tables 2.1 and 2.2 (NICNAS, 2008; HSDB, 2009; U.S. EPA, 2010).

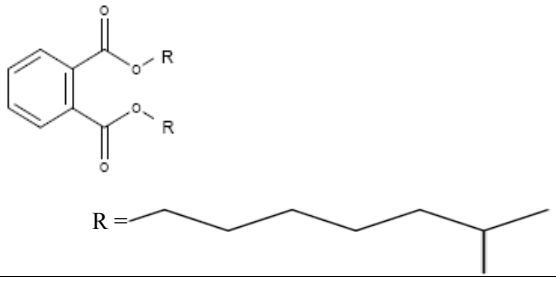
Table 2.1 Names, Structural Descriptors, and Molecular Formulas of DIOP (NICNAS, 2008)	
CAS Number:	27554-26-3
Chemical Name:	1,2-Benzenedicarboxylic acid, diisooctyl ester
Common Name:	Diisooctyl phthalate (DIOP)
Molecular Formula:	C24H38O4
Structural Formula:	
Molecular Weight:	390.62
Synonyms:	Diisooctyl 1,2-benzenedicarboxylate; Phthalic acid, diisooctyl ester
Purity/Impurities/Additives:	Technical grade reagent: 99%, mixture of C8 isomers, ≤2% dioctyl phthalate

Table 2.2 Physicochemical Properties of DIOP	
Property	**Value**
Physical state	Clear, viscous, oily liquid with a faint odor (NICNAS, 2008)
Melting point	-45°C (NICNAS, 2008); -50°C (U.S. EPA, 2010)
Boiling point	370°C (HSDB, 2009); 230°C (0.53 kPa) (NICNAS, 2008)
Density	986 kg/m3 (20°C) (NICNAS, 2008; HSDB, 2009)
Vapor pressure	1.33 kPa (200°C) (NICNAS, 2008)
Water solubility	0.00024-0.00249 mg/L (ECB, 2007); <0.1 g/L (20°C) (NICNAS, 2008: HSDB, 2008)
Partition coefficient n-octanol/water (log Kow)	7.73 (ECB, 2007); 8.39 (NICNAS, 2008; HSDB, 2009)
Henry's law constant	3.1 x 10^{-5} atm-cu m/mol (25ºC) (NICNAS, 2008; HSDB, 2009; U.S. EPA, 2010)
Flash point (closed cup)	227°C (HSDB, 2009)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

In general, DIOP is manufactured commercially in a closed system by catalytically esterifying phthalic anhydride with C_8 oxo-alcohols (isooctanol). As with other phthalates, the unreacted alcohols are recovered and reused, and the DIOP mixture is purified by vacuum distillation or activated charcoal. The purity of DIOP can achieve 99% or greater using current manufacturing processes (Esso, 2001). The remaining fraction of the DIOP commercial mixture is comprised of ≤ 2% dioctyl phthalate esters (e.g. DEHP; 117-81-7).

Supply

U.S. production of DIOP has been slowly declining since a peak of 14,000 metric tons in 1989. Recently, production declined from 11,000 metric tons (2005) to 10,100 metric tons (2008; Bizzari, 2007, 2009)). DIOP's proportion of the total phthalate market declined as well, from 1.8% (2005) to 1.7% (2008).

U.S. consumption (in metric tons) of DIOP closely follows decrements in production and percentages of total phthalate market. This suggests that most DIOP produced in the U.S. is utilized locally. Currently, ExxonMobil is the only producer of DIOP in the U.S. (Bizzari, 2007, 2009).

Production and consumption trends for Western Europe are similar to those in the U.S. Consumption of DIOP has declined from a historic high of 42,000 metric tons (1988) to 15,000 metric tons (2008). Interestingly, the relative percent of the total phthalate market is similar to that in the U.S. (1.7%), even though overall consumption figures in Western Europe are much higher (Bizzari, 2007, 2009).

Data on the production and consumption (or import and export) of DIOP in other countries either are not available or have been combined into multi-phthalate groups, and so are not useable for this report.

Use

The HMWPEs 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 lubricating oils (NICNAS, 2008). DIOP is generally used for insulation in building wire (HSDB, 2009). NICNAS (2008) reported that in Australia, DIOP is imported in rubber compounds for the manufacture of automotive hoses and parts (including truck bed linings at 5-20% v/v) and is distributed to various institutions and laboratories for biotechnological and pharmaceutical research. Other uses noted in HSDB (2009) are plasticizers for vinyl, cellulosic and acrylate resins, and synthetic rubber. In a study by the Danish Ministry of the Environment (DME, 2009), a shower mat contained 3100 mg/kg of bis (6-methylheptyl) phthalate (1330-91-2) in addition to other phthalates. The use of DIOP has also been reported in teethers (10.2%) and pacifiers (17.1%; Stringer, 2000). In the U.S., the FDA has approved DIOP for use in adhesives (21 CFR 175.105) or surface resin and polymer coatings (21 CFR 175.300) for products that have contact with food (products intended to be used in production, manufacturing, packing, transport, or holding of food).

4. TOXICOKINETICS

Twenty-four human volunteers were administered either a single control, low, or high dose of combined phthalate diesters (containing dibutyl phthalate [DBP], diethylhexyl phthalate [DEHP], butyl benzyl phthalate [BBP], and DIOP) labeled with isotope, spiked in margarine, and spread on toast (Anderson et al., 2001). The low dose included 168 µg of [^{13}C]-DIOP and 190–255 µg of each of the other phthalates, while the high dose included 336 µg of [^{13}C]-DIOP and 380–510 µg of each of the other phthalates. [^{13}C]-DIOP was 60% pure, with isooctylalcohol (used to synthesize the labeled compound) being the major impurity. The levels of excreted monoesters in the urine were measured by liquid chromatography-mass spectrometry (LC-MS) from samples collected 1 day prior to dosing and 1, 2, and 6 days following dosing. The study design was approved by an unspecified ethics panel. Monoesters for DEHP and DIOP co-eluted when analyzed by the LC protocol and were reported as the mean for the two octyl metabolites. The mono esters had excretion yields of 14% and 12% for the low and high doses, respectively, in the 24 hour urine collection (Anderson et al., 2001).

No labeled monoesters were detected in 2- and 6-day urine collections. Interestingly, background levels of the monoesters were detected in the urine of all volunteers at all sample points.

Sprague-Dawley rats, beagle dogs, and miniature pigs were administered DIOP in the diet at 50 mg/kg-day for 21–28 days prior to being administered a single radioactively [^{14}C]-labeled dose of DIOP in corn oil via gavage (Ikeda et al., 1978). Animals were sacrificed;

tissues (liver, lung, kidney, gastrointestinal tract, brain, muscle, and fat), urine, and feces were analyzed for [^{14}C] content at 4, 8, 24, and 96 hours (all species) and 21 days (dogs and pigs) after dosing with [^{14}C]-labeled DIOP. Radioactivity persisted in the gastrointestinal tract in all species for several days. In rats, approximately 50% of [^{14}C] activity was excreted in urine and the remaining 50% was excreted in the feces; nearly 85% of the dose was excreted within 24 hours and 100% within 4 days. In contrast, DIOP was primarily excreted in the feces in dogs (69–80%) and in the urine of pigs (65–86%), and excretion was slower in these species than in rats (complete excretion slightly >4 days in dogs and nearly 21 days in pigs). In each species, [^{14}C]-DIOP was distributed to body fat; however, distribution to lipid-rich tissues such as the brain and the lung was minimal. Additional data indicate that virtually all of the [^{14}C] in rat tissue and excreta 4 days after dosing was in the form of metabolites (metabolized DIOP as measured by the percentage of water-soluble radioactivity); in contrast, only 63 and 71% of [^{14}C] in dogs and pigs, respectively, had been metabolized in 4 days.

In another metabolism study (Calafat et al., 2006), four female Sprague Dawley rats (75 day old; 250 g) were administered 300 mg DIOP/kg via gavage. Urine was collected from each rat for analysis 24 hours before, just before, and 24 hours after DIOP administration. Collected urine was stored at -40C until analysis for mono-(3-carboxypropyl) phthalate (MCPP), mono-*n*-butyl phthalate (MBP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(3-methyl-5-dimethylhexyl) phthalate (MiNP), mono-(3-methyl-7-methyloctyl) phthalate (MiDP), and mono-*n*-octyl phthalate (MnOP) by the U.S. Centers for Disease Control and Prevention (CDC). Three metabolites (± standard deviatons) were detected in 24 hour urine samples, MCPP (1.9 ± 0.5 µg/mg creatinine), MnOP (1.9 ± 0.8 µg/mg creatinine), and MiNP (0.005 ± 0.004 µg/mg creatinine). For comparison, in the same experiment, DnOP administration (300 mg/kg gavage) resulted in the production of MCPP (225 ± 1.2 µg/mg creatinine) and MnOP (0.4 ± 0.2 µg/mg creatinine) metabolites. The author has suggested that detection of MCPP (and MnOP) following DIOP administration may be from contamination of the isomeric mix with DnOP or another linear chain phthalate.

5. HAZARD INFORMATION

This section contains brief hazard summaries of the adverse effects of DIOP in a variety of animal and bacterial species. When evaluating hazard study data, CPSC staff utilized the definitions for toxicity as presented in regulation (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 DIOP resulted in an oral LD_{50} = 2769 mg/kg in one mouse study, and >22,000 mg/kg in two other studies (rat and mouse). Dermal toxicity with LD50s > 3160 mg/kg were reported in two rabbit studies. DIOP was a severe dermal irritant at high doses in one well conducted rabbit study, but only a minimal to mild irritant in two other studies (rabbit and rat). There was inadequate evidence to determine if DIOP was an acute inhalation toxicant, a primary ocular irritant, a sensitizer, or a chronic toxicant. Studies provided were also inadequate to determine if DIOP was a carcinogen, reproductive toxicant, or developmental toxicant.

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 or less; *intermediate-term* or *subchronic*, 15 to 364 days; *long-term* or *chronic*, greater than 365 days; and *multigenerational*; ATSDR, 2007).

ACUTE DOSE TOXICITY

5.1. Acute Oral Toxicity

The acute oral LD_{50} for DIOP in rats is >22,000 mg/kg (NICNAS, 2008; ECB, 2000; Krauskopf, 1973). LD_{50}'s of 2769 mg/kg (GTPZAB, 1973) and >26,000 mg/kg (NICNAS, 2008) were identified for the mouse. No methodological or data details were located for the GPTZAB study, limiting its usefulness.

All of the acute rat and mouse oral LD_{50}'s cited for DIOP (except the GTPZAB study) were considerably higher than the oral LD_{50} range (50 to 5000 mg/kg) that is considered toxic in FHSA criteria.

The weight of evidence including sufficient animal data supported the conclusion that DIOP did not fit the definition of an "acute oral toxicant" when considering FHSA criteria (16 CFR §1500.3(c)(2)(i)(A)).

5.2. Acute Dermal Toxicity

Bio/dynamics (1981) reported no mortality among New Zealand white rabbits (2/sex/dose) exposed to DIOP at 50, 200, 794, or 3,160 mg/kg on intact clipped skin under occluded conditions for 24 hours and observed for 14 days. Compared to other treatment groups (there was no control group), body weight gain at day 14 was lower in rabbits dosed with DIOP at 3,160 mg/kg. No abnormal findings were reported at necropsy. Other studies reported dermal LD_{50} values >12,000 mg/kg in rabbits (UCDS, 1965; RTECS, 2010; ECB, 2000). No further details were located.

The weight of evidence including sufficient animal data supported the conclusion that DIOP did not fit the definition of an "acute dermal toxicant" when considering FHSA criteria (16 CFR §1500.3(c)(2)(i)(C)).

5.3. Acute Inhalation Toxicity

No information regarding the acute inhalation toxicity of DIOP was located.

The lack of studies supports the conclusion that there is "inadequate evidence" for the designation of DIOP as an "acute inhalation toxicant" when considering FHSA criteria (16 CFR §1500.3(c)(2)(i)(B)).

5.4. Primary Skin Irritation

In the Bio/dynamics (1981) study, New Zealand white rabbits (2/sex/dose) exposed to DIOP at 50, 200, 794, or 3,160 mg/kg on intact clipped skin under occluded conditions for 24 hours were monitored for erythema and other indications of skin irritation. The intensity and duration of skin irritation responses varied in a dose-related manner. Little to no erythema was noted in rabbits exposed to DIOP at 50 or 200 mg/kg. Erythema was slight to well-defined and lasted up to 3 days in animals exposed to 794 mg/kg. Erythema was slight to severe and persisted up to 7 days in animals exposed to 3,160 mg/kg. Other studies reported mild irritation resulting from application of DIOP to the skin in rabbits at 500 mg/kg in an unoccluded test (RTECS, 2010; ECB, 2000) and no irritation in male rats following single or repeated applications of undiluted DIOP (dose not specified) (ECB, 2000). No further details were located.

Study details demonstrated that high concentrations of DIOP were a primary skin irritant. The weight of evidence including sufficient animal data supported the conclusion that DIOP did not fit the definition of "corrosive" as outlined in the FHSA (16 CFR §1500.3(c)(3)), but did fit the definition as a "primary irritant" when considering FHSA criteria (16 CFR §1500.3(c)(4)). Slight to severe dermal erythema persisted for up to 7 days in animals dosed with 3160 mg/kg DIOP in tests that most closely fulfilled testing criteria as defined in 16 CFR §1500.41.

5.5. Primary Eye Irritation

One drop of the undiluted DIOP applied to the conjunctival sac did not cause eye irritation in rabbits (ECB, 2000). No further details were located.

The lack of study details supported the conclusion that there was "inadequate evidence" for the designation of DIOP as a "primary eye irritant" when considering FHSA criteria (16 CFR §1500.3(c)(4)).

5.6. Sensitization

No information regarding sensitization and exposure to DIOP was located. The lack of studies supported the conclusion that there was "inadequate evidence" for the designation of DIOP as a "sensitizer" when considering FHSA criteria (16 CFR §1500.3(c)(5)(i)).

REPEAT DOSE TOXICITY

Overall, a lack of comprehensive studies pertaining to particular organ systems or exposure durations (i.e. acute, subchronic, or chronic) prohibited the selection of a hazard endpoint for systemic toxicity. Limited experimental detail also prevented identification of no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) values for the studies presented. The lack of studies supported the conclusion that there was "inadequate evidence" for the designation of DIOP as a "chronic hazard" when considering FHSA criteria (16 CFR §1500.135).

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

Leather workers exposed to mixed phthalates (including periodic exposures to DIOP) for ≥6 years complained of pain, numbness, spasms of the hands and feet, polyneuritis, and ear effects (Milkov et al., 1973, as cited in NICNAS, 2008). Ambient air concentrations of phthalate mixtures of 1.7–66 mg/m^3 were reported. No further details were available.

The repeated-dose toxicity of DIOP was evaluated in several poorly reported animal studies. No effects were observed in rats dosed orally with 1,000 mg/kg-day DIOP for 8 days, as assessed by blood, post-mortem, and histological examinations (ICI Chemicals & Polymer, 1958, as cited in NICNAS, 2008). No effect on growth was reported in rats administered DIOP via the oral route at 0, 100 mg/kg-day (five generations for 21 months), 300 mg/kg-day (three generations for 21 months), or 500 mg/kg-day (three generations for 15 months) (Lefaux, 1972, as cited in NICNAS, 2008 and ECB, 2000). In studies conducted by the U.S. Food and Drug Administration (FDA), no effects were reported in rats or dogs dosed orally with 100 mg/kg-day DIOP for 4 or 14 weeks, respectively (Shibko and Blumenthal, 1973). No further details were provided.

5.8. Neurotoxicity

Hens (hybrid Rhode Island Red × New Hampshire Red; n = 4) were administered Fyrlube 22 (a mixture containing 70% t-butylphenyl phosphates, 20% DIOP, and 10% cresylic phosphates) at 5,000 mg/kg-day via gavage for 5 consecutive days and observed for 21 days following dosing (Cascieri, 1977). The study also included testing of several other phosphate ester products that did not include DIOP. An untreated control group was also included. Animals were observed for clinical signs of toxicity and neurotoxicity once daily at least 5 times/week for the duration of the study. Clinical signs of neurotoxicity were first observed 9–14 days after the initiation of dosing with Fyrlube 22. All four hens in this group exhibited paralysis beginning on days 14–17, and two of them subsequently died. Reductions in body weight were observed in all Fyrlube 22 hens over the course of the study; on average, these hens lost 32% of their body weight during the study. Similar results were reported for the other products tested, indicating that the observed neurotoxicity can be attributed to the phosphate esters in these products. There were no effects in controls.

The lack of comprehensive neurotoxicity studies using only DIOP as a test substance supported the conclusion that there was "inadequate evidence" for the designation of DIOP as a "neurotoxicant".

5.9. Reproductive Toxicity

Although the study by Lefaux (1972, as cited in NICNAS, 2008) described above included multigenerational exposure, it is unclear if reproductive toxicity endpoints were evaluated in this study (no data were provided).

The lack of comprehensive reproductive toxicity studies using DIOP as a test substance supported the conclusion that there was "inadequate evidence" for the designation of DIOP as a "reproductive toxicant."

5.10. Prenatal, Perinatal, and Post-natal Toxicity

The only available data on developmental effects come from a parenteral study, in which female rats were administered 0, 5, or 10 mL/kg DIOP (0, 4,930, or 9,860 mg/kg, using the reported density of 986 kg/m^3 [NICNAS, 2008]) on days 5, 10, and 15 of gestation by intraperitoneal injection (Grasso, 1981, as cited in ECB, 2000). No increase in fetal mortality or

skeletal abnormalities was observed. It was reported that there was a high incidence of soft tissue abnormalities in both treated groups, but quantitative data were not provided in the available summary.

The lack of comprehensive developmental toxicity studies using DIOP as a test substance supported the conclusion that there was "inadequate evidence" for the designation of DIOP as a "developmental toxicant".

5.11. Carcinogenicity

The lack of comprehensive carcinogenicity, genotoxicity, or initiation/promotion studies using only DIOP as a test substance supported the conclusion that there was "inadequate evidence" for the designation of DIOP as a "carcinogen".

Genotoxicity

DIOP tested negative for reverse mutation in assays using *Salmonella typhimurium* with or without metabolic activation (NICNAS, 2008; ECB, 2000; Goodyear Tire and Rubber Co., 1981). Although weak mutagenic activity was observed in a "modified" Ames test (not further described) in the presence (but not absence) of metabolic activation, the results were considered equivocal because responses were seen in a narrow concentration range and did not show a dose-response (Grasso, 1978, as cited in NICNAS, 2008).

Concentrated tannery effluent extracts containing DIOP and other organic compounds were tested for mutagenic activity in *S. typhimurium* strains TA97a, TA98, TA100, TA102, and TA104 and DNA repair-defective *Escherichia coli* K-12 strains AB1157, AB2463, AB2494, and AB3027 (Alam et al., 2010). DIOP was a major component of the effluent extracts. Concentrated and extracted effluents tested positive for mutagenicity (defined as a greater than twofold increase in revertant frequency) in one or more Ames tester strains and positive for genotoxicity in *E. coli* strains. These results are suggestive, but the effluent extracts are complex mixtures and the components responsible for their genotoxic activity are unknown.

Treatment with DIOP (99.9% pure) at concentrations ranging from 0.13 to 42.4 µg/mL did not induce the appearance of a significant number of transformed loci in a cell transformation assay in BALB/3T3 cells (Nuodex, Inc., 1981).

Initiation and Promotion

No initiation or promotion studies were located for DIOP.

Carcinogenicity Studies

No carcinogenicity studies were located for DIOP.

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 there may be a potential for formation of aerosol during some applications (OECD, 2004). Because HMWPEs are handled only in industrial manufacturing facilities and involves incorporation of the phthalate ester into a matrix, 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 DIOP were not found.

7. DISCUSSION

Toxicity data associated with DIOP are limited. No reliable NOAEL or LOAEL values for reproductive, developmental, or repeated dose systemic toxicity were identified.

8. REFERENCES

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