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CONSUMER PRODUCT SAFETY COMMISSION
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Memorandum

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SUBJECT : Toxicity Review of Di(isodecyl) Phthalate

This memo provides the U.S. Consumer Product Safety Commission's (CPSC's) Health Sciences staff assessment of the potential toxicity associated with di(isodecyl) phthalate (DIDP).

CPSC staff assesses a household 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 household substance must satisfy a two-part definition under 15 USC 1262 (f)(1)(A). First, the substance must be toxic as defined by the FHSA, or fall into one of the other hazard categories enumerated in the statute. Second, it must have the potential to cause "substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including ingestion by children." 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 hazardous substance appropriately according to the requirements of the FHSA.

These comments are those of the CPSC staff, have not been reviewed or approved by, and may not necessarily represent the views of, the Commission.

The first step in the risk assessment process is hazard identification, that is, a review of the available toxicity data for the chemical under consideration and a determination of whether the chemical meets the definition of "toxic" under the FHSA. CPSC staff assessed household substances for their ability to cause adverse chronic health effects (including carcinogenicity, neurotoxicity, and reproductive and developmental toxicity) using guidelines issued by the Commission (CPSC, 1992). If it is concluded that a substance is toxic under the FHSA 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" under the FHSA.

This memo represents the first step in the risk assessment process; that is, the hazard identification step. This toxicity review contains a summary of toxicity data available for DIDP, assesses the toxicity of DIDP based on the definitions in the FHSA, and includes acceptable daily intake levels (ADI) for sensitive endpoints.

Physiochemical Properties

DIDP is a phthalate that is a plasticizer and softener used in the polymer industry and is also categorized as a lubricant and additive. It is used in the manufacture of polyvinyl chloride and other vinyl products such as wire and cable, and has been found in children's toys (CPSC, 2001).

DIDP (CAS Numbers 68515-49-1 and 26761-40-0) is a complex mixture of branched C9-11 isomers containing mainly C10 isomers of $C_{28}H_{46}O_4$ (446.7 Da). It is created from a reaction of phthalic anhydride and isodecyl alcohol with an acid catalyst. Other synonyms for DIDP are Diplast R, Emkarte 1020, Hexaplas DIDP and Jayflex DIDP. DIDP is an organic, viscous, oily liquid (IUCLID, 2000). The structure and physical properties of DIDP are as follows:

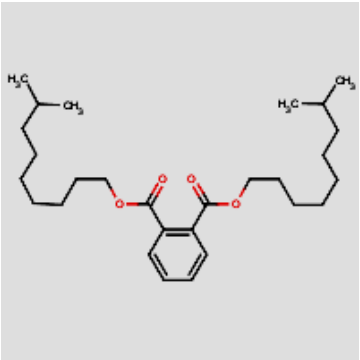

Figure 1: Structure of DIDP

Table 1: Physical Properties of DIDP

Melting Point	**approximately -50°C**
Boiling Point	**>400°C**
Relative Density	**0.971 g/cm^3 at 15°C**
Vapor Pressure	**5.1x 10-5 Pa at 25°C**
Partition Coefficient	**log Pow: 3-4**
Water Solubility	**not soluble, 1.19 mg/l**
Flash Point	**212°C**
Auto Flammability	**approximately 390°C**

Toxicokinetics

Dermally applied, DIDP is absorbed at a very low level. Two studies in rats show that only trace amounts (two to four percent) of applied ^{14}C-DIDP was absorbed into tissues or excreted (Midwest Research Institute, 1983; Scott et al., 1987).

In an oral study, rats were given 0.1, 11.2, or 1000 mg/kg ^{14}C-DIDP in corn oil by gavage. The reported absorbed levels after a 72-hour collection were 56, 46 and 17% respectively. The tissue level of DIDP was one percent, while 99% of the dose was collected from urine and feces at all doses. The highest level of absorbed radioactivity was seen in the gastrointestinal tract, liver and kidneys. The amount of radioactivity released in the feces was 57, 65 and 81% with increasing dose, and 41, 32 and 12% was released into the urine respectively (General Motors Research Laboratories, 1983).

In an inhalation study, rats were exposed to 91 mg/m^3 of ^{14}C-DIDP for six hours. Animals were sacrificed immediately and 72 hours after the exposure. The amount of DIDP absorbed into the body was 58%; 85% of that was in the lung and 12% was in the gut. Seventy-three percent of the radioactive dose was cleared after 72 hours, indicating that the absorption of DIDP via the inhalation route was about 73% (General Motors Research Laboratories, 1981).

The major routes of excretion of DIDP are via the urine and feces. Fecal excretion increased from 58% to 82% after oral administration of DIDP to rats with increasing dose (0.1- 1000 mg/kg). The remaining material was excreted in the urine. There is evidence of reduced excretion into the bile with increasing dose (14% down to 4.7% with dose increase from 0.1- 1000 mg/kg) (General Motors Research Laboratories, 1983).

DIDP is metabolized first to the relatively hydrophobic MiDP[1], and then metabolized to more hydrophilic oxidative metabolites that are excreted in the urine, similar to that seen with other high molecular weight phthalates such as DEHP, DINP and DNOP. The proposed metabolic pathway in rats is presented in figure 2 presented below (Kato et al., 2007). DIDP is rapidly

[1] See Abbreviations List in Appendix.

cleared with a half-time of approximately 14 hours. The secondary metabolites of hydrolytic monoesters predominate in the urine, with the major metabolite being MCiNP. Suitable biomarkers with specificity to DIDP are MCiNP, MHiDP, and MOiDP (Kato et al., 2007).

In a study of urinary metabolites of DINP, hydroxy- and oxo-metabolites of DIDP (MHiDP, MOiDP and MHiDP) were detected in rats dosed with DINP (CAS Number 68515-48-0 and CAS Number 28553-12-0), suggesting that DIDP was present in the DINP formulations used in this particular study (Silva et al., 2006).

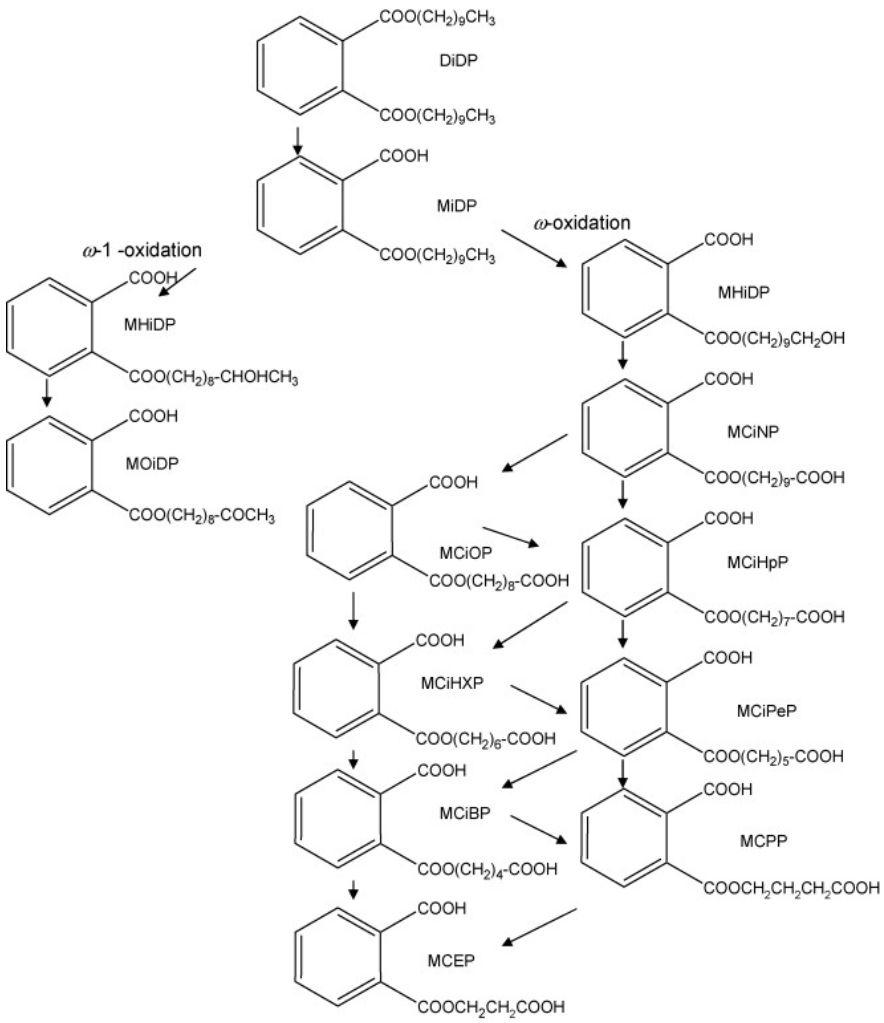

Figure 2. Proposed metabolic pathway of DIDP (Kato et al., 2007).

Exposure

DIDP exposure can occur via oral, dermal and inhalation routes. Occupational exposure can occur from inhalation and dermal routes, while consumers are exposed mainly from dermal and oral routes. Some known products that contain DIDP are listed in table 2. The manufacturers

exposure limit for DIDP is five mg/m^3 based on a value recommended by the American Conference of Governmental Industrial Hygienists (ACGIH®) (IUCLID, 2000).

The levels of several phthalate metabolites were measured in milk and milk products (e.g., infant formula) from areas around the world. Less than five µg/kg (or below the limit of detection) of DIDP was detected from these sources: raw milk, pasteurized and homogenized milk, yogurt with fruit, reconstituted infant formula from different parts of the world, and liquid infant formula from Europe (Sørensen, 2006).

DIDP was found in food wrap on the Brazilian market in high concentrations. This wrap was used with high fat-containing foods, which are susceptible to absorbing the plasticizer from the food wrap. Pork Italian sausage with 17% w/w fat content was packaged in wrap containing 11.6 $\pm$ 0.4% w/w content of DIDP. The packaging of a T-bone steak (with 16% fat w/w) contained 10.5 $\pm$ 2% DIDP. In both these cases, DIDP was found with di(2-ethylhexyl)phthalate (DEHP). The Brazilian government regulates the levels of phthalates in film packaging of fatty foods (greater than five percent w/w fat) to be not more than three percent w/w DIDP (Freire et al., 2006).

The estimated concentration of metabolites of DIDP were analyzed from 129 human urine samples. The hydrolytic monoester MIDP was not detected in any samples; however, the oxidative metabolites were present in most samples, suggesting that exposure to DIDP was prevalent. MCiNP, MHiDP, MOiDP were all detected in 98%, 96% and 85% of the samples in concentrations ranging from < 0.25 ng/mL for all metabolites to 334.5 ng/mL, 589.0 ng/mL, and 127.3 ng/mL, respectively. There was a correlation ($p<0.0001$) between the levels of DIDP metabolites and DINP urinary metabolites in these samples, suggesting a common source or parent product (Silva et al., 2007). In comparison, DIDP phthalate metabolite concentrations were lower than other analogous DINP and DEHP oxidative metabolites.

The following table contains the known uses of DIDP in the marketplace, industry, and for medical applications.

Table 2: Known Uses of DIDP.

Construction	Consumer	Medical
Polyvinyl chloride (PVC) film (NICNAS, 2008)	Artificial leather used in shoes, gloves, clothing (CERHR, 2003)	PVC hospital wristbands (Hills and Ive, 1993)
PVC sheet and coating products (NICNAS, 2008)	Pool lining (CERHR, 2003)	
PVC flooring (NICNAS, 2008)	Children's vinyl toys (CERHR, 2003)	

Construction	Consumer	Medical
PVC roofing (NICNAS, 2008)	Food Wrap (Freire et al., 2006)	
PVC car undercoating (NICNAS, 2008)	Molded PVC in footwear (NICNAS, 2008)	
PVC sealants (NICNAS, 2008)	Packaging materials (NICNAS, 2008)	
PVC hose (NICNAS, 2008)	Flame resistant plastics (NICNAS, 2008)	
Pressure sensitive adhesive (NICNAS, 2008)	Exercise balls (NICNAS, 2008)	
Printing inks (NICNAS, 2008)		
PVC wire and cable coating (NICNAS, 2008)		
Anti-corrosion and anti-fouling paints (NICNAS, 2008)		
Surfactant (NICNAS, 2008)		

Chronic Hazard Identification

In evaluating toxicity data, staff applies the definition for toxicity in the regulations (16 CFR §1500.3 (c)(2)(ii)) promulgated under the FHSA (15 U.S.C. 1261-1278) and chronic hazard guidelines (CPSC, 1992). A substance or mixture is classified as "known to be toxic" in humans only if there is sufficient evidence in humans, and is regarded as "probably toxic" if there is either limited evidence in humans or sufficient evidence in animals (summarized in table 3). If a substance is "known to be toxic" or "probably toxic" in humans it is considered "toxic" under the FHSA. If a substance is "possibly toxic", it would not be considered "toxic" under the FHSA.

Acceptable daily intake values (ADI) are calculated when a given chemical is considered "toxic" due to chronic effects 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. In some cases insufficient data are available to calculate an ADI.

Table 3: Classification of Chronic Hazards under the FHSA

Evidence	Human Studies	Animal Studies
Sufficient Evidence	**Known**[a]	**Probable**[a]
Limited Evidence	**Probable**[a]	Possible
Inadequate Evidence	Possible	---

a: Considered "toxic" under the FHSA.

Systemic Effects

LD_{50}[2] values with acute oral exposure of DIDP in rats were reported in two studies. The first study reported the LD_{50} to be greater than 29100 mg/kg and the second LD_{50} was greater than 62080 mg/kg (BASF, 1961; Smyth et al., 1962). The LC_{50}[3] in a 4 hour inhalation study performed on rats was greater than 12540 mg/m^3 (General Motors Research Laboratories, 1981).

In studies with repeated dosing of DIDP, the main effects were increased liver weights with correlating histological changes. There were also changes in kidney weight, and the testes may be a target as well. NOAEL[4] and LOAEL[5] levels from these studies are recorded in table 4 below. Details on these studies follow.

In a 21-day feeding study, Fischer 344 rats were fed 0, 0.3, 1.2, and 2.5% DIDP (300, 1000 or 2000 mg/kg/day as calculated by NICNAS, 2008) (BIBRA, 1986). There was a statistically significant decrease in weight in animals treated with 2.5% DIDP; only males showed a statistically significant decrease in food consumption. Significant increases were seen in absolute and relative liver weights and relative kidney weights in both sexes given 1.2% or 2.5% DIDP. Cyanide-insensitve palmitoyl-CoA oxidation (which increases with increased peroxisomal oxidation (Ishii et al., 1980)) was significantly increased in animals treated with 1.2% and 2.5% DIDP. Histologic examination showed variable increases in the number and size of hepatocyte peroxisomes in animals treated with 2.5% DIDP. Relative testes weights were significantly increased in males at 2.5% DIDP, however, no atrophy was observed. A NOAEL was recorded at 300 mg/kg/day for females, and a LOAEL was set at 300 mg/kg/day in males based on increased absolute and relative liver weight at 1000 mg/kg/day and above (BIBRA, 1986).

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[2] Lethal dose in 50% of a population.

[3] Lethal concentration in 50% of a population.

[4] No Observable Adverse Effect Level.

[5] Low Observable Adverse Effect Level.

In a 28-day feeding study, male Fischer 344 rats were fed 0, 0.02, 0.05, 0.1, 0.3 and 1% DIDP (approximately 25, 57, 116, 353, and 1287 mg DIDP/kg/day as calculated by Lake et al.). There was a statistically significant increase in relative liver weight at 0.1% and absolute liver weights at 0.3% DIDP. A statistically significant increase in liver palmitoyl-CoA oxidation activity was seen at 0.1% DIDP. There were no observed changes in body weight and there were no histological changes in the testes. A NOAEL was reported by CERHR at 116 mg/kg/day and a LOAEL at 353 mg/kg/day for increased liver weights and increased cyanide-insensitive palmitoyl-CoA oxidation (Lake et al., 1991).

In a three-month study, Sprague Dawley rats were fed 0, 800, 1600, 3200, and 6400 ppm DIDP (approximately 55, 100, 200, and 400 mg/kg/day for males and 60, 120, 250, and 500 mg/kg/day for females as calculated by NICNAS, 2008). Relative liver weights were significantly increased in all males; absolute liver weights were significantly increased only in males at 6400 ppm. In females, relative and absolute liver weights were significantly increased at $\geq$ 1600 ppm and $\geq$ 3200 ppm respectively. Relative kidney weights were significantly increased at all treated doses in males. In females, relative kidney weights were significantly increased in a non-dose dependent manner at 1600 ppm and 3200 ppm, but not at 6400 ppm. There were no observed pathological abnormalities. A NOAEL was reported by CERHR at 200 mg/kg/day for males and 120 mg/kg/day for females (BASF, 1969; CERHR, 2003).

In a three-month feeding study, 20 Charles River CD rats were given 0, 0.05, 0.3, or 1% DIDP (approximately 28, 170, and 586 mg/kg/day for males and 35, 211, and 686 mg/kg/day for females as reported by Hazelton). Absolute and relative liver weights were significantly increased in both sexes at 1% DIDP (586 and 686 mg/kg/day for M and F). Relative kidney weights were significantly increased in males at 0.3% and 1% DIDP (170 and 586 mg/kg/day). There were no effects on food consumption, body weight, or clinical chemistry. There were no histological changes in liver, kidney or testes. A NOAEL was reported as 170 and 211 mg/kg/day for males and females respectively. The LOAEL was 586 and 686 mg/kg/day for males and females respectively for increased liver weight (Hazelton, 1968a).

In a 13-week diet study, Beagle dogs (3 male and 3 female per group) were given 0, 0.3, 0.5, or 1% DIDP (approximately 0, 15, 75 and 300 mg/kg/day as calculated by NICNAS). Three dogs given 1% DIDP showed slight to moderate weight loss. There was a dose related increase in absolute liver weights, but was not statistically significant based on the small study size. There was also a non-significant slight elevation in liver to body weight ratios in five out of six dogs at 1%. Moderate swelling and vacuolation of hepatocytes were observed in four dogs in each group given 0.5% and 1% DIDP. There were no effects observed in food consumption, hematology, clinical chemistry and urinalysis. Testicular lesions were not observed. A NOAEL of 15 mg/kg/day was reported based on increased liver weights and histological changes. A LOAEL was reported at 75 mg/kg/day for increased liver weight and slight to moderate swelling and vacuolation of hepatocytes. Given the small study size, statistics were not performed (Hazelton, 1968b).

An inhalation study exposed Sprague Dawley rats to 505 mg/m^3 DIDP vapor for two weeks, six hours per day for five days per week. No systemic effects were reported (General Motors Research Laboratories, 1981).

In summary, subchronic studies (see table 4) show that the liver was a target of DIDP. Effects included increased liver weight, increased peroxisomal enzyme levels and histological changes (swelling and vacuolation of hepatocytes). The kidney was also affected by DIDP as an increase in kidney weight was observed. The testes do not seem to be a target in these subchronic studies as there were no observed histological abnormalities; however, in one study there was a significant increase in relative testes weight with high dose DIDP. Subchronic studies typically begin after acquisition of puberty and effects on testes are dependent upon both duration and time of exposure. Therefore, further studies need to be completed to determine if exposure prior to puberty may affect the testes. **DIDP is considered to be a probable toxicant based on systemic effects.**

Table 4: Subchronic Animal Studies.

Route of Exposure, Duration, Protocol	Species / #	DIDP Exposure % (mg/kg/day)	NOAEL mg/kg/day	LOAEL mg/kg/day	Reference
Diet, 21 day	Rat, 5/sex/dose	0, 0.3, 1.2, 2.5 % (0, 300, 1000, 2000 mg/kg/day)	F: 300	M 300: ↑ liver weight (absolute and relative)	BIBRA, 1986
Diet, 28 day	Rat 5/sex/dose	0, 0.02, 0.05, 0.1, 0.3, 1 % (0, 25, 57, 116, 353, 1287 mg/kg/day)	116	353: ↑ liver weights, ↑ cyanide-insensitive palmitoyl-CoA oxidation	Lake et al., 1991
Diet, 3 months	Rat 20/sex/dose	0, 800, 1600, 3200, 6400 ppm (M: 0, 55, 100, 200, 400 mg/kg/day F: 0, 60, 120, 250, 500 mg/kg/day)	M: 200 F: 120	M 400: ↑ liver weights (absolute) F 250: ↑ liver weights (relative)	BASF, 1969

Route of Exposure, Duration, Protocol	Species / #	DIDP Exposure % (mg/kg/day)	NOAEL mg/kg/day	LOAEL mg/kg/day	Reference
Diet, 3 months	Rat 10/sex/dose	0, 0.05, 0.3, 1% (M: 0, 28, 170, 586 mg/kg/day F: 0, 35, 211, 686 mg/kg/day)	M:170 F: 211	M 586:, ↑ absolute and relative liver weight F 686:, ↑ relative and absolute liver weight	Hazelton Laboratories, 1968a
Diet, 13 weeks	Dog 3/sex/dose	0, 0.3, 0.5, 1 % (0, 15, 75, 300 mg/kg/day)	15	75: ↑ liver weight, slight to moderate swelling and vacuolation of hepatocytes	Hazelton Laboratories, 1968b
Hersh-berger Assay Oral gavage 10 days with 0.4 mg/kg/day testost-erone	Rat,SD Crl:CD Male Castrated prepubertal 6/group	(0, 20, 100, 500 mg/kg/day)	M: 100	500: ventral prostate and seminal vesicle weight compared to testosterone positive control	Lee and Koo, 2007 (discussed under developmental effects)
Inhalation, 2 weeks, 6 h/d, 5 d/wk	Rat 8 Male	0, 505 mg/m^3	M: 505 mg/m^3	No systemic effects	General Motors Research Laboratories, 1981

Dermal and Ocular Effects

Two studies performed by BASF AG were summarized by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2008; BASF, 1979a; BASF, 1979b). Undiluted DIDP (0.5 mL) was placed on rabbit's skin under an occlusive dressing for 24 hours. In the first study, mild skin erythema and mild edema occurred and persisted from two to eight days. Dermal LD_{50}'s were estimated to be greater than 2910 mg/kg in the rat and 3160 mg/kg in the rabbit (Inveresk Research International, 1981; Industrial Bio-test Laboratory, 1975; Hazelton Laboratories America, 1978).

Several human patch tests have been performed with DIDP. The first test applied undiluted DIDP to the skin (under an occlusive dressing for 24 hours) to 15 subjects with no signs of irritation (Hill Top Research, 1995). Kanerva et al. performed patch tests in an occupational dermatology clinic with five percent DIDP. In the first study, two of 144 patients exhibited an irritation reaction and in the second, two of 310 patients treated with five percent DIDP under occlusion for two days exhibited irritant reactions (Kanerva et al., 1996; Kanerva et al., 1999).

Four rabbit studies have been performed to determine if DIDP is irritating to the eye and are detailed in the NICNAS review. In summary, undiluted DIDP applied to the eye led to slight redness of the conjunctiva that lasted at least 24 hours in all rabbits. There was no corneal opacity observed. One study was performed to OECD test guidelines. In this study, undiluted DIDP (0.1 mL) was applied to the eyes, leading to redness of the conjunctiva after one hour that resolved after 24, 48 and 72 hours (Industrial Bio-test Laboratories, 1975; BASF, 1979a; Inveresk Research International, 1981; BASF, 1986).

In summary, DIDP caused mild skin irritation and mild redness of the conjunctiva with ocular exposure. Table 5 gives more detail on the dermal and ocular studies.

Table 5: Summary of Dermal and Ocular Studies.

Route of Exposure/ Duration	Species / #	DIDP exposure	Result	Reference
Dermal/ 24 hrs	Rabbit / 6	Undiluted DIDP, 0.5 mL under occlusive dressing	Mild skin erythema in all animals after 24 hrs. Mild oedemal in 3/6 animals. Skin irritation until day 2, cleared by day 8	BASF, 1979c
Dermal/ 24 hrs	Rabbit / 4	Undiluted DIDP, 0.5 mL + 0.5-1% bisphenol A under occlusive dressing	Skin erythema in all animals after 24 hrs. Erythema cleared after 2 days	BASF, 1979b
Dermal	Rabbit		LD_{50}>3160mg	Industrial Bio-test Laboratory, 1975
Dermal	Rabbit		LD_{50}>3160mg	Hazleton Laboratories America, 1978
Dermal	Rat		LD_{50}>2910mg	Inveresk Research International, 1981

Route of Exposure/ Duration	Species / #	DIDP exposure	Result	Reference
Dermal/ 24 hrs	Human / 15	Undiluted DIDP under occlusive dressing	No signs of irritation up to 24 hrs.	Hill Top Research, 1995
Dermal / 2 days	Human / 310	5% (w/w) DIDP dissolved in petrolatum under occlusive dressing	2 patients exhibited irritation after application	Kanerva et al., 1999
Ocular	Rabbit / 6	Undiluted DIDP	Slight redness of the conjunctiva in all animals after 1, 4, and 24 hrs. Cleared at 48 and 72 hrs.	Industrial Bio-test Laboratories, 1975
Ocular	Rabbit/ 6	Undiluted DIDP 0.1 mL	Slight redness of the conjunctiva in all animals after 1, 4, and 24 hrs. after 72 hrs redness of conjunctiva observed in 3/6 animals	BASF, 1979a
Ocular	Rabbit/ 6	Undiluted DIDP 0.1 mL	Slight redness of conjunctiva in all animals after 1, 4, and 24 hrs. Clear after 48 and 72 hrs.	Inveresk Research International, 1981
Ocular **OECD test guidlelines**	Rabbit/ 3	Undiluted DIDP 0.1 mL	Redness of the conjunctiva in all animals after one hour, no reactions noted after 24, 48, or 72 hrs.	BASF, 1986

Sensitization

Three sensitization tests were performed in guinea pigs, and are detailed in the NICNAS review (Inveresk Research International, 1981; Huntington Research Centre, 1994; Exxon Biomedical Sciences, 1992). See table 6 for a summary of DIDP sensitization studies. Only one study

showed positive results. It was a Buehler study that reported a positive response after rechallenge with DIDP on day 35. Seven of 20 animals showed well-defined erythema (score two), and one showed slight erythema.

Two human skin sensitization studies have also been completed. In the first, a patch test of undiluted DIDP treatment three times a week for three weeks reported no positive skin reactions in 104 human subjects (Medeiros et al., 1999 as cited in CERHR 2003 and NICNAS 2008). The next study was an irritant and allergic human patch test with five percent DIDP. Two of 144 subjects exhibited irritation and none showed an allergic reaction (Kanerva et al., 1996).

Contact allergic dermatitis from DIDP was reported in a 64 year old woman who reacted with severe vesicular eczema on both wrists under two PVC wristbands. When tested, she showed a positive reaction with five percent DIDP (Hills and Ive, 1993).

In summary, one of three animal studies showed positive skin reactions to rechallenge with DIDP. Human subjects tested with DIDP for sensitization did not show allergic reactions; however, there is a single human case report of an allergic dermatitis in response to PVC wristbands containing DIDP (Hills and Ive, 1993). These results suggest that DIDP is not a strong sensitizer.

Table 6: Summary of DIDP Sensitization Studies.

Type of Study	Species / #	DIDP Exposure	Result	Reference
Magnussun and Kligman maximization study	Guinea Pig / 20	Undiluted DIDP	Negative. Positive result in control.	Inveresk Reserch International, 1981
Buehler study	Guinea Pig / 20	Undiluted DIDP	Day 35 rechallenge: 8/20 animals slight erythemal, 7/20 well-defined erythema. 1/20 control animals also showed slight erythema at rechallenge.	Exxon Biomedical Sciences, 1992
Buehler study	Guinea Pig / 20	Undiluted DIDP	Negative.	Huntington Research Centre, 1994

Type of Study	Species / #	DIDP Exposure	Result	Reference
Skin patch test	Human / 104	Undiluted DIDP applied three times a week for three successive weeks	Lack of positive skin reactions.	Medeiros et al., 1999
Irritant and allergic patch test	Human / 144	5% (w/w) DIDP dissolved in petrolatum under occlusive dressing	2 subjects exhibited skin irritant reactions, none showed allergic reactions.	Kanerva et al., 1996

Reproductive Effects

In previously discussed animal repeated dose studies, testicular lesions were not reported in doses up to 2000 mg/kg/d (BIBRA, 1986).

Two multi-generational animal studies were completed by Exxon Biomedical Sciences and were published by Hushka et al., 2001. The studies are summarized in table 8. In the first study (study A) Crl:CD BR-VAF/Plus (Sprague Dawley) rats from Charles River Laboratories (30/sex/dose) were given 0, 0.2, 0.4, or 0.8% DIDP in their diet for ten weeks prior to and during mating. Females continued to receive DIDP throughout gestation and lactation. In parental F_0 adults, there were significant reductions of bodyweight gain and food intake at the 0.8% dose during gestation and lactation in females. There was a significant decrease in body weight of F_1 parental adult males in the 0.4% and 0.8% DIDP groups. In F_1 parental females, there was a significant decrease in body weight at postpartum days ten and 14. Kidney and liver body weight ratios were significantly increased in all adult F_0 and F_1 treated parental males and females treated only with 0.4% and 0.8% DIDP. There were histological changes observed in the liver and kidney of F_0 and F_1 parental adults. Liver observations included centrilobular or diffuse hepatocellular hypertrophy (as seen with peroxisome proliferation). In the male adult kidneys, there was accumulation of eosinophilic granular cytoplasmic pigment in cortical tubules, cortical tubular degeneration, and increased incidence of granular casts in renal tubules in the males treated with 0.8% DIDP. There were no histopathologic changes seen in the kidneys of DIDP treated females. There was a small but significant increase in the age at vaginal opening in F_1 offspring treated with 0.4% and 0.8% DIDP. The left ovary weight was significantly decreased in F_1 0.8% treated parental adults. Relative testes, epidydimis and seminal vesicle weight were significantly increased versus the control weights in F_1 treated males; however, there were no pathologic changes in sexual organs. There was a small but significant decrease in normal sperm in all treated groups. There was a significant reduction in the length of the estrous cycle in F_0 females in the 0.8% dose group. There were no effects in either generation on mating, fertility, or gestational indices (mean length of gestation and mean

litter size). The NOAEL for fertility was 0.8% (600 mg/kg/day as calculated by Hushka et al. 2001).

In the second multi-generational study (study B), Crl:CD BR-VAF/Plus (Sprague Dawley) rats from Charles River Laboratories (30/sex/dose) were given 0, 0.02, 0.06, or 0.2 or 0.4% DIDP in the diet for 10 weeks from before mating and during mating. Treatment of the females was continued throughout gestation and lactation (Hushka et al., 2001). The protocol was similar to study A; however, lower doses were chosen to establish a NOAEL, and dose groups 0.2% and 0.4% were repeated to test the reproducibility of offspring survival effects in the F_2 generation (discussed in detail under Developmental Effects). In the parental F_0 generation, there were significant increases in the liver and kidney weight at the 0.4% dose. The F_1 offspring survival or body weight parameters were not significantly affected. In the F_1 parental males, significant increases in kidney to body weight ratios were seen at 0.2% and 0.4%; the females showed significant increases at 0.2% DIDP. In parental F_1 females at 0.2 and 0.4% and parental F_1 males at 0.4%, there were increases in liver to body weight ratios. There were no effects on mating, fertility, fecundity, or gestational indices. F_1 and F_2 offspring did not show differences in age of vaginal opening. There were no histological lesions or weight changes in the reproductive organs of either sex. The NOAEL for fertility was set at 0.4% by the authors (233-635 mg/kg/day for males and 271-645 mg/kg/day for females as calculated by CERHR, 2003).

In summary, reproductive effects of DIDP include a significant decrease in ovary weight and significant increases in relative testes, epididymis and seminal vesicle weight without histological changes. There was a non-reproducible increase in age of offspring vaginal opening. There were no effects on mating, fertility, or gestational indices in any generation. There was a small but significant decrease in the number of normal sperm of treated males, and an increase in the length of the estrous cycle in the F_0 females treated with 0.8% DIDP.

Developmental Effects

A one generational comparative developmental screening test was performed on Wistar rats (seven to ten pairs/dose). DIDP, at doses of 0, 40, 200, and 1000 mg/kg/day, was given by gavage two weeks prior to mating for a total of 29 days for males or until post natal day six for females (BASF, 1995; Hellwig et al., 1997). The dams and fetuses were examined on gestational day 20. Fetuses were examined for weight, external, visceral and skeletal malformations. Maternal toxicity was observed in the high dose group (1000 mg/kg/day) with significantly reduced feed consumption, significantly increased absolute and relative liver weight and vaginal hemorrhage in three dams. Maternal kidney weight was unaffected. There were increases in fetal variations (rudimentary cervical and/or accessory 14^{th} ribs) per litter (24.3, 37.2, 38.4, and 44.2% in the control, 40, 200 and 1000 mg/kg/day groups respectively) reaching statistical significance at 200 and 1000 mg/kg/day. There was an increased incidence of dilated

renal pelves[6] and hydroureter in all treatment groups. The Expert Panel for the Center for the Evaluation of Risks to Human Reproduction (CERHR, 2003) set the developmental NOAEL at 40 mg/kg/day and the maternal NOAEL at 200 mg/kg/day.

In a second one-generational developmental study, Sprague-Dawley rats (25/dose) were given DIDP by gavage at 0, 100, 500, or 1000 mg/kg/day from gestational day six to 15 (Waterman et al., 1999). Maternal toxicity was seen at 1000 mg/kg/day with significantly decreased weight gain and food consumption, although a significant increase in body weight gain from gestational days 15-18 may indicate a recovery effect. Effects on fetal mortality or weight were not seen. Cesarean section data did not indicate any developmental toxic effects; the mean numbers of corpora lutea, total implantation sites, post implantation loss and viable fetuses of treated animals were comparable with controls. Fetal body weight and sex ratios were not affected. DIDP did not produce external, visceral or skeletal malformations; however, there was evidence of increased fetal variations. A dose-related increase in percent fetuses with a supernumerary (7^{th}) cervical rib and incidence of rudimentary lumbar (14^{th}) ribs was observed and was statistically significant at 500 mg/kg/day (on a per fetus basis) and 1000 mg/kg/day (on a per litter and fetus basis). This study was examined by the Expert Panel for the CERHR (2003) that set the developmental NOAEL at 100 mg/kg/day based on the significant incidence of cervical and accessory 14^{th} ribs on a per fetus basis at 500 mg/kg/day. Waterman reanalyzed the data, agreed with the new lower NOAEL level, and also provided the panel with benchmark doses below (table 7).

Table 7: Benchmark doses (95% CI) at the five percent excess risk level.

	Benchmark dose (95% CI) mg/kg/day
Rudimentary lumbar ribs	188 (169)
Skeletal variants	258 (238)
Supernumerary cervical ribs	645 (515)

Two multi-generation studies were completed by Exxon Biomedical Sciences and were published by Hushka et al., 2001. In the first study (study A) Crl:CD BR-VAF/Plus (Sprague Dawley) rats from Charles River Laboratories (30/sex/dose) were given 0, 0.2, 0.4, or 0.8% DIDP in their diet for ten weeks prior to and during mating. Females continued to receive DIDP throughout gestation and lactation. There was significantly decreased F_1 pup survival at birth and on postnatal day (pnd) four in the 0.8% treatment group. In the F_2 generation, there was a significant decrease in pup survival in all treatment groups on pnd one and four. This decrease in pup survival was also observed on pnd seven and at weaning in the high dose group. Postnatal body weight gain was reduced at the high dose in F_1 and F_2 pups. Liver weight (mean relative) was increased in F_1 male pups at 0.8%, and F_1 female pups at 0.4 and 0.8%. Hepatic

[6] Dilation of the renal pelvis and hydroureter (dilation of the ureter) are a physiologic response to the interruption of the flow of urine.

hypertrophy and eosinophilia were seen in F_1 and F_2 pups at 0.4 and 0.8%. A developmental NOAEL was not established due to decreased pup survival at all doses in the F_2 offspring generation. The 0.2% dose (131-152 mg/kg/day and 162-319 mg/kg/day in F_0 and F_1 dams during gestation and lactation respectively as calculated by Hushka et al.) was identified as the developmental LOAEL.

In the second two-generation study (study B), Crl:CD BR-VAF/Plus (Sprague-Dawley) rats from Charles River Laboratories (30/sex/dose) were given 0, 0.02, 0.06, or 0.2 or 0.4% DIDP in the diet for ten weeks before mating and during mating, and treatment of the females was continued throughout gestation and lactation (Hushka et al., 2001). In the F_1 pups, there were no effects on survival, body weight gain, organ weight, ano-genital distance, nipple retention, perputial separation, or vaginal opening. In the F_2 pups there was significantly decreased pup survival on pnd one and four at 0.2 and 0.4% DIDP. In the F_2 generation, significantly decreased pup body weight was observed at 0.2% and 0.4% on pnd 14 (females) and pnd 35 (males). There were no differences in anogenital distance or nipple retention of the F_2 pups. The age of preputial separation was increased by 1.2 days in the F_2 pups at 0.4% DIDP but the difference was not statistically significant. Overall NOAEL and LOAEL for offspring survival effects were 0.06% and 0.2% respectively (approximately 50 mg/kg/day and 165 mg/kg/day as calculated by Hushka et al.). A developmental NOAEL was set at 0.06% by the authors (38-44 mg/kg/day and 52-114 mg/kg/day during pregnancy and lactation respectively as calculated by Hushka et al., 2001).

Cross-fostering and switched diet studies were completed to determine if postnatal developmental effects in pups were due to lactational transfer. Twenty CRl:CDBR VAF Plus rats per group were fed 0 or 0.8% DIDP for ten weeks prior to mating through gestation and lactation. For the cross-fostered study, pups from ten treated dams were switched with pups from ten control dams. After weaning, the diet of the pups continued as per dam exposure. For the diet switch portion of the study, pups from control dams were fed the DIDP diet after weaning, and pups from the treated dams were given the control diet after weaning. Results show that control pups switched to a 0.8% DIDP fed dam had significantly lower body weight on pnd 14 and 21 due to lactational exposure. Pups exposed to DIDP *in utero* but nursed by a control dam did not show body weight changes. In the switched diet study, pups exposed to DIDP *in utero* and while nursing recovered body weight after receiving control diets after weaning (Hushka et al., 2001).

In a Hershberger assay, castrated rats were treated with DIDP and testosterone to test for antiandrogenic effects. Castrated prepubertal SD Crl:CD rats (six per group) were given 0, 20, 100, and 500 mg/kg/day DIDP by gavage in combination with 0.4 mg/kg/day testosterone. Treatment with 500 mg/kg/day DIDP led to a significant decrease in ventral prostate and seminal vesicle weight compared to the testosterone positive control. DIDP, therefore, does possess antiandrogenic activity. At 500 mg/kg/day DIDP there was also a significant increase in liver weight. The NOAEL for this study was set at 100 mg/kg/day (Lee and Koo, 2007).

In summary, DIDP treatment led to increased incidences of minor skeletal variations. Offspring survival was affected and decreased pup body weight was observed at 0.2 and 0.4% DIDP in

the F_1 and F_2 generations. **DIDP is considered a probable toxicant under the FHSA based upon these developmental effects.**

Table 8: Summary of Reproductive and Developmental Studies.

Type of Study	Species/#	DIDP Exposure	NOAEL	LOAEL	Reference
Reproductive					
Multi-generational	Crl:CD BR-VAF/Plus rats 30/sex/dose	0, 0.2%, 0.4%, 0.8% in diet	600 mg/kg/day fertility		Hushka et al., 2001
Multi-generational	Crl:CD BR-VAF/Plus rats 30/sex/dose	0, 0.02%, 0.06%, 0.2%, 0.4% in diet	F:233-635 mg/kg/day fertility M:271-645 mg/kg/day fertility		Hushka et al., 2001
Developmental					
One-generation	Wistar rats 7-10 pair/dose	0, 40, 200, 1000 mg/kg/day by gavage	40 mg/kg/day 200 mg/kg/day maternal	200 mg/kg/day fetal variations	Hellwig et al., 1997
One-generation	Sprague Dawley rats 25/dose	0, 100, 500, 1000 mg/kg/day by gavage	100 mg/kg/day developmental	500 mg/kg/day incidence of cervical and accessory 14th ribs	Waterman et al., 1999
Multi-generation	Crl:CD BR-VAF/Plus rats 30/sex/dose	0, 0.2%, 0.4%, 0.8% in diet	Not set	Offspring survival, ↓pup bw 131-152 mg/kg/day during gestation 162-319 mg/kg/day during lactation	Hushka et al., 2001
Multi-generation	Crl:CD BR-VAF/Plus rats 30/sex/dose	0, 0.02%, 0.06%, 0.2%, 0.4% in diet	50 mg/kg/day offspring survival	165 mg/kg/day offspring survival	Hushka et al., 2001

Genotoxicity/Carcinogenicity

In the available genotoxicity studies (see table 9), DIDP treatment led to negative results in *in vitro* bacterial mutation assays, *in vitro* mouse lymphoma assays and in an *in vivo* mouse micronucleus assay.

Positive results were seen in one of two *in vitro* transformation assays. DIDP was tested on Balb/c-3T3 mouse cells at concentrations up to 20 μL/mL. The cells were exposed for 72 hours and then incubated for four weeks. There were no significant increases in transforming activity. Balb/3T3 Clone A31 mouse embryo cells were also treated with DIDP for 20-24 hours then incubated from four to six weeks. DIDP led to an increase in transforming frequencies at one μL /mL but not at 0.01 or 0.1 μL/mL (Barber et al., 2000).

Table 9: Summary of genotoxicity studies with DIDP.

	Test: Species/Strain	Dose	Metabolic Activation	Result	Reference
In vitro					
Reverse mutation	*s. typhimurium* TA98, TA100, TA1535, TA1537	100-1000 μg/plate	With and without	Negative	Zeiger et al., 1985
Reverse mutation	*S. typhimurium* TA100	Not reported	Not Reported	Negative	Seed, 1982
Mouse lymphoma mutation assay	L5178Y $TK^{+/-}$ mouse lymphoma cells	-S9:2000-10000 nl/mL +S9: 250-10000 nl/mL	With and without	Negative	Hazelton Biotechnologies Company, 1986
Mouse lymphoma mutation assay	L5178Y $TK^{+/-}$ mouse lymphoma cells	-S9: 2-10 μL/mL +S9: 0.25-2 μL/mL	With and without	Negative	Barber et al., 2000
In vivo					
Micronucleus test	CD-1 mice (bone marrow)	Single oral (gavage) dose of 0, 1250, 2500 or 5000 mg/kg	N/A	Negative	Hazelton Washington, 1994

In a two-year oral toxicity/carcinogenicity study of DIDP (table 10), Fischer 344 rats were exposed to 0, 400, 2000 and 8000 ppm DIDP (calculated by Cho et al. as 0.85, 4.13, 17.37 mg/kg/day for males and 0.53, 3.03, 13.36 mg/kg/day for females) to study the

potential peroxisome proliferation activity of DIDP. The animals were sacrificed after two years, organ weights were measured and microscopic examinations performed. At 8000 ppm there was a significant decrease in the overall survival and body weight with a significant increase in relative liver and kidney weights in males and females. However, there were no treatment related neoplastic lesions observed in internal organs including the liver of either sex. There was an increased incidence of mononuclear cell leukemia; however, this is a common neoplasm in F344 rats and the incidence was not outside the historical ranges in control animals.

For assessment of peroxisome proliferation, 50 rats were fed 0, 400, 2000, 8000 ppm DIDP and 12000 ppm di(2-ethylhexyl)phthalate (DEHP, as a positive control) and sacrificed at 12 weeks and 32 weeks. After 12 weeks of treatment, the levels of catalase in the 8000 ppm DIDP were increased compared to controls, yet after 32 weeks there were no differences in the catalase levels and activity. In the positive DEHP treated control animals, catalase levels and activity were increased at both 12 and 32 weeks. Peroxisome proliferators increase the levels of enzymes in the peroxisomal fatty acid β-oxidation system leading to the generation of hydrogen peroxide. Peroxisome proliferation is thought to be hepatocarcinogenic in rats[7]. In this study, DIDP induced early catalase levels, but failed to maintain the catalase-inducing potential after two years. Therefore, long term exposure to DIDP results in limited peroxisomal proliferating activity (Cho et al., 2008).

Table 10: Summary of *in vivo* Carcinogenicity studies.

Route/ Duration	Strain/#	DIDP Exposure	Result	Reference
Oral /Two Year	Fischer 344 rat	0, 400, 2000, 8000 ppm DIDP (Males: 0.85, 4.13, 17.37 mg/kg/day Females: 0.53, 3.03, 13.36 mg/kg/day)	8000 ppm: significant decrease in survival and body weight. No treatment related neoplastic lesions observed in internal organs.	Cho et al., 2008

[7] There is no evidence for the relevancy of the hepatocarcinogenic processes in humans (CPSC, 2001; Klaunig et al., 2003).

Route/ Duration	Strain/#	DIDP Exposure	Result	Reference
Oral / 12 and 32 weeks	Fischer 344 rat / 50	0, 400, 2000, 8000, ppm DIDP (Males: 0.85, 4.13, 17.37 mg/kg/day Females: 0.53, 3.03, 13.36 mg/kg/day)	8000 ppm: Increase of catalase activity above control after 12 weeks, no increase after 32 weeks.	Cho et al., 2008

In summary, positive results were observed in one *in vitro* transformation assay (Barber et al., 2000). In a two year rat study, neoplastic lesions were not observed in the liver. The peroxisome proliferation activity of DIDP was not maintained over the course of the two year study (Cho et al., 2008). **DIDP, therefore, is not considered to be carcinogenic.**

Discussion

In animals DIDP is absorbed at a very low level through the skin or when ingested. Dermal studies in rabbits showed two to four percent absorption, and oral studies in rats showed one percent absorption. When inhaled, DIDP is more readily absorbed, with a level of around 73%. DIDP may cause mild skin irritation, and may cause mild redness of the conjunctiva with ocular exposure (BASF, 1986). Subjects tested with DIDP for sensitization did not show allergic reactions; however, there is a human case report of an allergic dermatitis in response to wristbands containing DIDP (Hills and Ive, 1993). These results together suggest that DIDP is not a strong sensitizer. DIDP shows low acute toxicity with LD_{50} levels >2910 mg/kg for dermal exposure, >29100 mg/kg for oral exposure and >12540 mg/m^3 for inhalation exposure.

Subchronic studies show an increase in liver weight, and an increase in the levels of peroxisomal enzymes with histopathologic changes of swelling and vacuolation of hepatocytes (Hazelton, 1968b). Table 4 lists NOAEL and LOAEL levels for liver effects in response to DIDP. DIDP is considered to be a probable toxicant based on systemic effects**. An ADI based on liver effects calculated from the lowest NOAEL (15 mg/kg/day) divided by a safety factor of 100 [10 (animal to human) x 10 (sensitive populations)] is 0.15 mg/kg DIDP.**

There were also significant increases seen in relative kidney weight in several studies. BIBRA 1986, a 21-day rat study, reported an increase in relative kidney weight in both sexes when given 1000 or 2000 mg/kg/day. BASF 1969, a three-month rat study, reported significant increase in relative kidney weight in males at all doses (55-400 mg/kg/day) and in females at 120 mg/kg/day and 250 mg/kg/day. There were no pathological abnormalities noted. Hazelton 1968a, a three-month rat study, reported significant increase in relative kidney weight in males

at 170 mg/kg/day and 586 mg/kg/day with no observed histological changes in the kidney. The BASF 1969 study observed a significant increase in relative kidney weight at 55 mg/kg/day. The lowest kidney LOAEL is in a two-year carcinogenicity study; the treatment of 8000 ppm DIDP (13.36 - 17.37 mg/kg/day for females and males respectively), led to a significant increase in relative kidney weights in males and females (Cho et al., 2008). **An ADI calculated from this dose [13.36 – 17.37 mg/kg/day / 10 (lowest dose safety factor) / 10 (sensitive population safety factor] is 0.13-0.17 mg/kg DIDP based on kidney effects.**

Carcinogenicity of DIDP has been evaluated in several studies and results suggest that DIDP is not carcinogenic or mutagenic. All genotoxic tests with DIDP resulted in negative results. One of two *in vitro* cell transformation tests was positive for transforming potential. Also, a two-year oral carcinogenic study looked at the peroxisome proliferation potential of DIDP. While the results showed an increase in liver weight, there were no relevant liver neoplastic lesions observed after two years of exposure. The liver peroxisome proliferation potential of DIDP was increased after three months into the study; however, long term results were negative. This suggests that DIDP, unlike other tested phthalates such as DEHP, does not maintain proliferation potential after long term exposure. These liver peroxisome proliferation effects observed in the rat are not relevant to humans (CPSC, 2001; Klaunig et al., 2003). DIDP is not considered to be carcinogenic.

In two two-generational reproductive studies, parental F_0 and F_1 animals showed statistically significant reduction in body weight with increased liver and kidney weight in response to DIDP. Also seen were the following: significantly reduced ovary weight; significant increase in age of vaginal opening; and significant increase in relative testis, epidydimis and seminal vesicle weight. There were also small significant decreases in levels in normal sperm and increase in the estrous cycle of F_0 females. There were no observed histological changes in sexual organs. There were also no effects in either generation on mating, fertility, fecundity, and pregnancy indices. The NOAEL for fertility was 0.4% (a calculated range of 233-645 mg/kg/day; Hushka et al., 2001). A Hershberger assay suggests that DIDP may be antiandrogenic, as observed by a decrease in ventral prostrate and seminal vesicle weight compared to the testosterone controls. DIDP is considered to be a probable toxicant based on reproductive effects. **A reproductive ADI based on fertility using the range 233-645 mg/kg/day divided by the safety factor of 100 [10 (rat to human) x 10 (sensitive population)] is 2.3 – 6.5 mg DIDP/kg**.

Developmental studies led to maternal toxicity at 1000 mg/kg/day. Statistically significant fetal variations were observed including rudimentary (14^{th}) cervical ribs and supernumary (7^{th}) ribs above 200 mg/kg/day. Decreased pup survival was also observed in the F_1 and F_2 generation, along with decreased weight in the F_2 pups. The lowest developmental NOAEL was 40 mg/kg/day based on the incidence of fetal variations (cervical and/or supernumary ribs variations). DIDP is considered to be a probable toxicant based on developmental effects. **A developmental ADI using this dose of 40 mg/kg/day divided by the safety factor of 100 [10 (animal to human) x 10 (sensitive population)] is 0.4 mg DIDP/kg**.

In evaluating the potential hazards presented by phthalates, the Commission staff has appropriately followed the definitions for toxic (both acute and chronic), irritant, and strong

sensitizer in the FHSA and its implementing regulations 16 CFR Part 1500. At this time, there is insufficient information for the staff to conduct the second part of the analysis to determine what, if any, risk would present due to DIDP in children's toys and child care articles.

CPSC staff concludes that DIDP may be considered a "probable toxicant" in humans by the oral route, based on sufficient evidence of systemic, reproductive and developmental effects in animals. Therefore DIDP has the potential to be toxic. In order to determine whether a DIDP-containing toy or child care article would be considered a hazardous substance under the FHSA, it must be determined that in any customary or reasonably foreseeable handling or use, a consumer would be exposed to DIDP in a way that presents a significant risk of the substantial health effects associated with it. A quantitative assessment of exposure and risk must therefore be performed to determine whether household substances containing DIDP may present a hazard to consumers. Such substances would be considered hazardous substances under the FHSA only if oral exposure during 'reasonably foreseeable handling and use' were to exceed the lowest ADI of 0.13 – 0.18 mg DIDP/kg.

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Abbreviations

ADI: Acceptable daily intake

DEHP: di(2-ethylhexyl)phthalate

DIDP: di(isodecyl) phthalate

DINP: di-disononyl phthalate

DnOP: di-*n*-octyl phthalate

FHSA: Federal Hazardous Substances Act

LD_{50}: Lethal dose to 50% of population

LC_{50}: Lethal concentration to 50% of population

LOAEL: Low adverse effect level

MBP: Mono-*n*-Butyl phthalate

MCEP: Mono(carboxy-ethyl) pththalate

MCiBP: Mono(carboxy-isobutyl) phthalate

MCiHpP: Mono(carboxy-isohexyl) pththalate

MCiOP: Mono(carboxy-isooctyl) pththalate

MCiPeP: Mono(carboxy-isopentyl) pththalate

MCiNP: Mono(carboxy-isononyl) pththalate

MCPP: Mono-(3-carbxoypropyl) phthalate

MEHP: Mono-(2-Ethylhexyl) phthalate

MHiDP: Mono(hydroxyl-isodecyl) pththalate

MIDP: monoisodecyl phthalate

MiNP: Mono-(3-Methyl-5-Dimethylhexyl) phthalate

MiDP: Mono-(3-Methyl-7-Methyloctyl) phthalate

MnOP: Mono-*n*-Octyl phthalate

MOiDP: Mono(oxo-isodecyl) pththalate

NOAEL: No adverse effect level

pnd: post-natal day

ppm: parts per million

PVC: Polyvinyl chloride