National Toxicology Program
U.S. Department of Health and Human Services

Center For The Evaluation Of Risks To Human Reproduction

NTP-CERHR EXPERT PANEL REPORT

on

DI ISODECYL PHTHALATE

OCTOBER, 2000 **NTP-CERHR-DIDP-00**

PREFACE

The National Toxicology Program (NTP) and the National Institute of Environmental Health Sciences established the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) in June, 1998. The purpose of the Center is to provide timely, unbiased, scientifically sound evaluations of human and experimental evidence for adverse effects on reproduction, including development, caused by agents to which humans may be exposed.

The following seven phthalate esters were selected for the initial evaluation by the Center: butyl benzyl phthalate, di(2-ethylhexyl) phthalate, di-isodecyl phthalate, di-isononyl phthalate, di-n-butyl phthalate, di-n-hexyl phthalate, and di-n-octyl phthalate. Phthalate esters are used as plasticizers in a wide range of polyvinyl chloride-based consumer products. These chemicals were selected for the initial evaluation by the CERHR based on their high production volume, extent of human exposures, use in children's products, published evidence of reproductive or developmental toxicity, and public concern.

This evaluation is the result of three public Expert Panel meetings and 15 months of deliberations by a 16-member panel of experts made up of government and non-government scientists. This report has been reviewed by the CERHR Core Committee made up of representatives of NTP-participating agencies, by CERHR staff scientists, and by members of the Phthalates Expert Panel. This report is a product of the Expert Panel and is intended to (1) interpret the strength of scientific evidence that a given exposure or exposure circumstance may pose a hazard to reproduction and the health and welfare of children; (2) provide objective and scientifically thorough assessments of the scientific evidence that adverse reproductive/development health effects are associated with exposure to specific chemicals or classes of chemicals, including descriptions of any uncertainties that would diminish confidence in assessment of risks; and (3) identify knowledge gaps to help establish research and testing priorities.

The Expert Panel Reports on phthalates will be a central part of the subsequent NTP report that will also include public comments on the Panel Reports and any relevant information that has become available since completion of the Expert Panel Reports. The NTP report will be transmitted to the appropriate Federal and State Agencies, the public, and the scientific community.

The NTP-CERHR is headquartered at NIEHS, Research Triangle Park, NC and is staffed and administered by scientists and support personnel at NIEHS and at Sciences International, Inc., Alexandria, Virginia.
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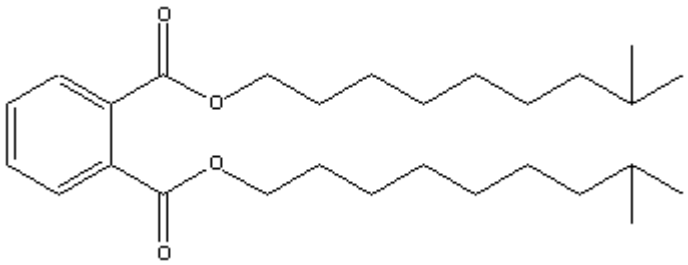
Diisodecyl Phthalate

1.0 CHEMISTRY, USAGE, AND EXPOSURE

1.1 Chemistry

Figure 1: Chemical Structure of a Diisodecyl Phthalate Isomer (Di-(8-methylnonyl) phthalate)



Commercial diisodecyl phthalate (DIDP) is a complex substance that is assigned two CAS Registry Numbers (26761-40-0 and 68515-49-1) (*1*). A synonym is 1,2-benzenedicarboxylic acid, di-C9-11branched alkyl esters, C10 rich. DIDP is manufactured by reaction of phthalic anhydride and isodecyl alcohol in the presence of an acid catalyst (*1*). The alcohol manufacturing processes are stable (essentially the same feed stock, propylene, and butene), so although the substances are complex, they are not variable (*1*). DIDP is an oily, viscous liquid at standard temperature and pressure.

Table 1: Physicochemical Properties of DIDP

Property	**Value**
Chemical Formula	$C_{28}H_{46}O_4$ (average)
Molecular Weight	447
Melting Point	-48 ^oC
Boiling Point	370 ^oC
Specific Gravity	0.97
Solubility in Water	Insoluble (<0.001 mg/L)
Log K_{ow}	~10

(*2*)

1.2 Exposure and Usage

Humans may be exposed to DIDP by the oral, dermal, and inhalation routes of exposure. Occupational exposure occurs primarily through inhalation and dermal contact, while consumer exposure occurs primarily by oral and dermal routes.

Occupational Exposure

DIDP, like other phthalate esters, is manufactured within a closed system that is under negative pressure. However, some exposures may occur during the loading and unloading of railroad cars and trucks. Somewhat higher exposures may occur during the production of polyvinyl chloride (PVC) products because of elevated temperatures and more open processes. The American Chemistry Council (ACC, formerly CMA) (*1*) cites six studies that indicate that exposures are below 1 mg/m^3 during production of phthalates and below 2 mg/m^3 during production of PVC. As discussed in Section 2.2, dermal exposure is not expected to result in significant absorption into the body.

Consumer exposure

The range of products that contain DIDP is quite broad. The amounts produced and the use categories for DIDP in 1998 are given in the Table 2.

Table 2: Calculated 1998 US Consumption of DIDP
(thousands of metric tons)

End Use	Subtotal	Total
Film and Sheet		20
Skins – Unsupported	7	
Pool Lining	9	
Other	4	
Artificial leather		20
Coated Fabrics		1
Dip Coating/Slush Molded		4
Toys	2	
Traffic Cones	<2	
Other	~1	
Tubings		9
Wire and Cables		45
Under-body Coating		36
GRAND TOTAL		135

(*1*)

Since DIDP, like other phthalates, is not bound in PVC, it can be released throughout the lifecycle of a product. Some end products do not result in direct consumer contact but may contribute to releases into the environment. Such uses include automobile undercoating, building materials, wires, and cables (*1*). Products which humans may contact directly include shoes, carpet backing, pool liners, and gloves (*1*). Direct exposure may also occur through food as a result of uptake by food animals, certain vegetables, and migration of DIDP from food packaging.

Food. DIDP was not detected in 74 samples of composite fatty foods from the UK at a detection limit of 0.01 mg/kg (*3*). These retail samples consisted of carcass meat, meat products, offal, poultry, eggs, fish, fats and oils, milk, and milk products. DIDP was not detected in 39 samples of infant formula from the UK at an

analytical limit of 0.1 mg/kg (*4*). In an earlier study (*5*), DIDP was not detected in 59 samples of 15 different brands of infant formula analyzed at a typical detection limit of 0.01 mg/kg wet weight. Because DIDP concentrations in foods and infant formulas were below detection limits in the surveys conducted by Ministry of Agricultural Fisheries and Food (MAFF) (*3-5*), the ACC (*1*) considered dietary exposure to humans negligible. The results of sampling infant formulas for phthalates by the US Food and Drug Administration (*6*) suggests that phthalates are present in lower frequency and concentrations in the US than in Europe.

Toys. In a Dutch survey of teething rings and toy animals, DIDP levels were measured at a concentration of 1.4–15% (*7*). Surveys conducted by the UK government found DIDP in 6 of 18 toys in 1990, 4 of 27 toys in 1991, 0 of 16 toys in 1992, and 0 of 29 toys in 1996 (*7*). In a Danish survey of 17 children's toys, those without PVC did not contain phthalates. DIDP was detected in 4 of the 7 PVC toys (3 teethers and 1 doll) at concentrations ranging from 0.7 to 10.1% by weight. Higher concentrations of DINP were also present. Precision measuring concentration is somewhat uncertain because the analytical method used (gas chromatography) did not cleanly resolve the peaks for DIDP and DINP (*8*). The Consumer Product Safety Commission (CPSC) did not detect DIDP in a sample of 35 toys that contained PVC. DINP was the predominant phthalate found. Although not specifically stated, the analytical methodology (GC/MS) used should have identified DIDP if present; lower levels of several phthalates were detected in some samples (*9*).

Exposure Estimate

Based on the physicochemical characteristics of DIDP and limited monitoring data, the Expert Panel believes it reasonable to assume that exposure to DIDP in the general adult population is lower than exposure to DEHP, which is estimated at 3–30 µg/kg bw/day (*10*). While no *in vitro* or *in vivo* data on DIDP leaching from toys are available, it is reasonable to postulate exposures several-fold higher than the general population in infants and toddlers who mouth DIDP-containing products.

The summary for Section 1 is located in Section 5.1.1.

2.0 GENERAL TOXICOLOGICAL AND BIOLOGICAL PARAMETERS

2.1 General Toxicity

Oral

The British Industrial Biological Research Association (BIBRA) (*11*) administered groups of 5 male and 5 female F344 rats (41–44 days old) dietary concentrations of 0, 0.3, 1.2, and 2.5% DIDP for 21 days. The authors calculated daily intake of DIDP as 0, 304, 1,134, and 2,100 mg/kg bw/day for males and 0, 264, 1,042, and 1,972 mg/kg bw/day for females. A fifth group was given diets containing 1.2% DEHP which corresponded to 1,077 mg/kg/day for males and 1,002 mg/kg bw/day for females. The level of cyanide-insensitive palmitoyl-CoA oxidation was determined. At necropsy, clinical chemistry was conducted, and liver, kidney, and testes weights were recorded and the organs were preserved in 10% formalin for histologic examination.

There was a significant reduction in food consumption and mean body weight in male rats fed 2,100 mg/kg bw/day beginning on day 3 and continuing throughout the study (69–82% of control). In female rats fed 1,972 mg/kg bw/day, mean body weight was reduced beginning on day 10 and continuing throughout the

study (83–87% of control). Absolute and relative liver weights were significantly increased at all doses in males and at the two highest doses in females. In males, absolute weights were 121, 186, and 172% of controls at low to high doses, respectively, and relative weights were 121, 201, and 254%, respectively. In females receiving the two highest doses, absolute weights were 160 and 192% of controls and relative weights were 176 and 238%, respectively. In low-dose males, absolute and relative weights were 121% of controls. A variety of other effects were observed at the two highest doses; these included a reduction in hepatocyte cytoplasmic basophilia in both sexes, an increase in eosinophilia (high dose only), reduced serum triglycerides and cholesterol levels in males (no dose-response relationship was apparent), and a significant increase in cyanide-insensitive palmitoyl-CoA oxidation in both sexes. There was a significant increase in the 11- and 12-hydroxylation (11- and 12-OH) of lauric acid (all treated males), and in the 12-OH level in females at the high dose of DIDP. Electron microscopic examination of hepatic peroxisomes showed a marked but variable increase in size and number in both sexes at the high dose, but the response was less marked in females. There was a significant decrease in kidney weight in both sexes at the high dose, but no histological changes were observed. Absolute testes weights were slightly, but significantly, reduced at 2,100 mg/kg bw/day, but relative testes weights were greater than controls; no histological changes were observed.

This study provides evidence that the liver is a target organ of DIDP. A similar pattern of effects noted with DEHP is seen: increased liver weight, induction of hepatic peroxisome proliferation, depressed serum triglycerides and cholesterol levels, and increased activity of hepatic metabolizing enzymes. The testes do not appear to be a target organ at these dose levels. The study provided a LOAEL of 1,042 mg/kg bw/day in females and 304 mg/kg bw/day in males. A NOAEL of 264 mg/kg bw/day was identified for females but no NOAEL was identified for males due to increased liver weight and 11- and 12-OH activity at all dose levels.

In a 4-week study (*12*), groups of 5 male F344 rats (42 days old) were given dietary concentrations of 0, 0.02, 0.05, 0.1, 0.3, or 1.0% DIDP (made up of equal parts Hexaplas [ICI], Jayflex [Exxon], and Palatinol Z [BASF]). These dose levels were reported to correspond to doses of 0, 25, 57, 116, 353, and 1,287 mg/kg bw/day. Another group was given a diet of 1% DEHP. Food consumption and body weights were recorded twice weekly. At necropsy, organ weights were recorded, cyanide-insensitive palmitoyl-CoA oxidation activity was measured, and tissues were preserved in formalin for histologic examination. At doses of 116 mg/kg bw/day and higher, there was a significant increase in relative liver weight, and at doses of 353 mg/kg bw/day and higher, absolute liver weights were significantly increased. The cyanide-insensitive palmitoyl-CoA activity was significantly increased at doses of 353 mg/kg bw/day and higher. Testes weight was not affected by treatment and there were no histological changes.

The study provides evidence that the liver is a target organ of DIDP and the effects seen are consistent with those observed with other studies of DIDP and with DEHP. The testes do not appear to be a target. The study provides a LOAEL of 353 mg/kg bw/day and a NOAEL of 116 mg/kg bw/day.

BASF (*13*) administered groups of 20 male and 20 female Sprague-Dawley rats dietary concentrations of 5,000 or 10,000 Palatinol Z for 28 days. This corresponded to average daily doses of 600 and 1,250 mg/kg bw/day for males and 1,100 and 2,100 mg/kg bw/day for females. A control group of 10 males and 10 females was fed the basal diet. Blood samples were taken from 5/sex/group on day 14 or 15 for hematological assessment and urinalysis was conducted on day 23 or 24. At necropsy, liver, kidney, and heart weights were recorded, and the liver and kidneys were examined histologically. Absolute and relative liver weights were significantly increased at both dose levels in both sexes, but there were no histologic changes. No other effects were noted.

Based on this 28-day study, BASF (*14*) administered groups of 20 male and 20 female Sprague-Dawley rats dietary concentrations of 800, 1,600, 3,200, or 6,400 ppm DIDP (Palatinol Z) for 90 days. These levels were equivalent to average daily doses of 55, 100, 200, and 400 mg/kg bw/day for males and 60, 120, 250,

and 500 mg/kg bw/day for females, respectively. A control group of 10 males and 10 females was fed the basal diet. An additional group was fed the 6,400 ppm diet for 90 days, followed by a recovery period of 21 days. Hematology and urinalysis were conducted on days 32–36 and 74–78. At necropsy, liver, kidney, and heart weights were recorded, and the tissues were preserved in 10% formalin. In male rats, there was a slight lag in body weight gain in the 100, 200, and 400 mg/kg bw/day groups from day 77 onward. This finding was still present in the 400 mg/kg bw/day group following the 21-day recovery period. In males, absolute liver weights were significantly increased at the highest (400 mg/kg bw/day) dose and relative liver weights were significantly higher in all groups; this effect persisted after the recovery period. In females, absolute liver weights were significantly increased at 250 and 500 mg/kg bw/day, and relative liver weights were significantly increased at doses of 120 mg/kg bw/day and higher. Relative kidney weights were significantly increased in males in all groups and in females at 120 and 250, but not 500, mg/kg bw/day doses. No histological lesions were noted in testes, ovaries, liver, or kidneys.

The study offers support that the liver is a target organ of DIDP based on liver weight, but not histological, changes. The testes do not appear to be a target. A NOAEL in males of 200 mg/kg bw/day was assumed since an increase in absolute liver weight was reported at the highest dose. In females, a NOAEL of 120 mg/kg bw/day was assumed based on increased absolute and relative liver weights at the two higher doses.

Hazelton (*15*) administered groups of 10 male and 10 female Charles River CD rats dietary levels of 0, 0.05, 0.3, or 1% DIDP for 90 days. Based on body weights, rats were assumed to be young adults. Based on food intake rates and body weights reported by authors, doses of 0, 28, 170, and 586 mg/kg bw/day and 0, 35, 211, and 686 mg/kg bw/day were calculated for males and females, respectively. At necropsy, clinical chemistry was conducted, organ weights were recorded, and the tissues were preserved in 10% formalin. There were no significant effects on food consumption, body weights, or clinical chemistry. Absolute and relative liver weights were significantly increased at the high dose in both sexes. Relative kidney weights were significantly increased in males at the two higher doses. There were no histologic changes in the testes, liver, or kidney. A minimal increase in thyroid activity was observed at the highest dose level; the activity was judged to be higher when the follicles were more uniform and smaller in size with a lighter colloid along with a tall cuboidal or columnar epithelium.

The study provides confirming evidence that the liver is a target organ of DIDP. The testes do not appear to be a target as no testicular lesions were observed in the high-dose group. The study provides a LOAEL of 586(M)–686(F) mg/kg bw/day and a NOAEL of 170(M)–211(F) mg/kg bw/day.

Hazelton (*16*) administered groups of 3 male and 3 female young adult beagle dogs dietary levels of 0, 0.05, 0.3, or 1% DIDP for 90 days. Based on food intake rates and body weights reported by authors, doses of 0, 15, 77, and 307 mg/kg bw/day and 0, 16, 88, and 320 mg/kg bw/day were calculated for males and females, respectively. There were no effects on food consumption, hematology, clinical chemistry (including ALT, AST, and BSP clearance), or urinalysis. Testicular lesions were not observed in microscopic slides prepared from Bouin's-fixed testes in high-dose dogs. Three dogs (2 male, 1 female) in the 307–320 mg/kg bw/day group showed slight-to-moderate weight loss. At necropsy, there was a dose-related increase in absolute liver weights, but the small sample size precluded statistical analysis. The mean liver weights were 253, 248, 274, and 317 g (males) and 190, 212, 220, and 287 g (females) for the 0, 0.05, 0.3, and 1% groups, respectively. The authors also reported a slightly elevated liver to body weight ratio in 5 of 6 dogs at the highest dose tested. Swollen and vacuolated hepatocytes were noted in two mid-dose males, two mid-dose females, one high-dose male, and three high-dose females. The Expert Panel concluded that the small sample size in this study precludes the determination of a NOAEL. A LOAEL of 77(M)–88(F) mg/kg bw/day was identified based on liver effects.

Inhalation

General Motors Research Laboratories (*17*) exposed 8 adult male Sprague Dawley rats by inhalation (aerosol) to 505 mg/m^3 (MMAD: 0.98µm) 6 hours/day, 5 days/week for 2 weeks. There were six control rats. After a subsequent 3-week observation period, the rats were killed and necropsied. There were no clinical signs of toxicity or effects on body weight. Effects in the lungs included a moderate increase in the width of alveolar septa with slight interstitial mixed inflammatory reactions, alveolar macrophages and type II pneumocytes were increased in number, and the peribronchial lymphoid tissue appeared slightly more prominent. No histological changes were noted in the liver, kidney, or spleen.

2.2 Toxicokinetics

Phthalate Moiety

Absorption

Rodents: Dermal
Dermal absorption of phthalates decreases with increasing side chain length beyond four carbons (*18*). In rats, 80% of dermally applied ^{14}C-DIDP (ring-label) was recovered at the site of application 7 days after the application. Only 2% of the applied dose was recovered in other tissues or excreta with a total recovery of only 82% reported. In another study in rats in which total recoveries were better (94% or greater) (*19*), similar results were obtained. ^{14}C-DIDP was applied to the skin and the dose site was occluded. At 1, 3, and 7 days, 96, 92, and 93% of the doses, respectively, were still at the application site. Only trace amounts of radioactivity were found in other tissues and excreta. The total absorbed dose was approximately 4% of the administered dose. DIDP dermal absorption has not been tested in humans, but an *in vitro* study conducted with DEHP suggests that the DIDP absorption rate through human skin is likely lower than the absorption rate for rat skin (*20*). Studies conducted by Deisinger et al. (*21*) have demonstrated that dermal absorption of DEHP from a plasticized film is slower than dermal absorption of neat DEHP. It is reasonable to assume that these results apply to DIDP.

Rodents: Oral
A study (*22*) conducted in rats evaluated the effect of oral dose on the toxicokinetics of ^{14}C-DIDP (labeled carboxyl groups). The doses, which were administered by gavage in corn oil, were 0.1, 11.2, or 1,000 mg/kg bw. The amounts absorbed can be estimated from the total radioactivity excreted in urine and bile or retained in the carcass at the end of 72 hours, and were 56, 46, and 17% for the low, medium, and high doses, respectively. The remainder of the radiolabeled activity was excreted in the feces with evidence, from bile radioactivity, of some enterohepatic uptake. The study indicated that at low doses at least 56% of orally-administered DIDP is absorbed. The data suggest partial saturation of DIDP metabolism by esterases in the gut in rats within the dose range administered in the study (0.1–1,000 mg/kg).

Rodents: Inhalation
Six male Sprague Dawley rats were exposed for 6 hours by inhalation (head only) to 91 mg/m^3 of ^{14}C-DIDP (*17*). Excreta were collected over a 72-hour period and 3 animals were analyzed for radioactivity immediately after the exposure and at 72 hours after the exposure. Assuming a minute volume of 200 mL for the rats, the estimated total amount of DIDP inhaled would be approximately 14.4 µmoles. The initial body burden was 8.3 µmoles, indicating that approximately 58% of what was inhaled was retained in the body. Twelve percent of the initial body burden was in the gut and 85% was in the lung. Seventy-three percent of the dose to the lung was cleared during the first 72 hours, indicating that absorption of DIDP or its metabolites from the lung into the rest of the body was about 73%.

Biotransformation

Bacterial
Ejlertsson et al. (*23*) reported no degradation of DIDP by microorganisms in a laboratory scale landfill reactor during 100 days of incubation.

Rodent
In rats orally administered ^{14}C-DIDP (*22*), the major metabolites detected in urine were phthalic acid and the oxidized monoester derivative, but no DIDP or monoisodecyl phthalate (MIDP) were detected over a wide range of doses (0.1–1,000 mg/kg). The relative amounts of each metabolite varied with dose with the monoester derivative increasing with increasing dose from 52% at the low dose to 72% at the high dose, while the phthalic acid decreased from 38 to 18%. The monoester oxidized derivative, MIDP, and DIDP were all detected in feces in dose-dependent amounts. The parent compound increased from 30 to 55 and 60% after doses of 0.1, 11, and 1,000 mg/kg, and the percentage of the oxidative derivative of the monoester and of MIDP at the same doses were, respectively, 25 and 30%, 14 and 26%, and 13 and 13%. The data suggest a metabolic scheme comparable to the one reported for DEHP, that is, de-esterification to the monoester form and an alcohol moiety by pancreatic lipase and intestinal mucosa esterase prior to absorption. The high content of MIDP in feces is consistent with such a scheme. The data also suggest saturation of the metabolism of DIDP in rats at a dose lower than 11 mg/kg.

Distribution

In studies conducted in rodents by either the oral (*22*) or the dermal (*18*) route, there was limited distribution to the tissues. Seven days after dermal administration, only trace amounts of DIDP were left in the body and showed no specific tissue distribution. Three days after oral administration of doses up to 1,000 mg/kg, less than 1% of the DIDP was found in the tissues. Following inhalation (*17*), the major sites of DIDP-derived material were the lung and the gut immediately after exposure. The next highest levels were found in the liver, kidney, and brain. At 3 days following administration, 27, 8, 9, and 10% of the initial burdens in the lung, gut, liver, and kidney remained. No DIDP-derived material was left in the brain after 3 days.

Excretion

In all studies in rodents, the major routes of excretion for absorbed DIDP are via the urine and feces. In orally-administered DIDP, fecal excretion increased from 58% of the total body burden at a dose of 0.1 mg/kg to 82% at a dose of 1,000 mg/kg. The remaining material was excreted in urine with less than 1% of the dose remaining in the animal after 3 days. There is evidence of excretion into the bile; the percentage of total administered dose that was recovered in bile decreased with increasing dose from 14% at a dose of 0.1 mg/kg to 4.7% at a dose of 1,000 mg/kg.

In rats exposed by inhalation, 45 and 41% of the absorbed dose were excreted via urine and feces, respectively. The excretion via the urine indicated an elimination half-life of 16 hours, with an elimination rate constant K_e of 0.042/hour. The elimination half-life for all routes of excretion (rate of decline in body burden) was 26 hours with an elimination rate constant of 0.027/hour.

Side Chain-associated Toxicokinetics

A major metabolite of DIDP, MIDP, is further oxidized.

2.3 Genetic Toxicity

The mutagenicity of DIDP has been examined in a number of bacterial (*24-26*), mammalian cell, and cell transformation assays. A bone marrow micronucleus test in CD-1 mice has also been performed (*27*). A recent OECD meeting (*28*) accepted the following conclusions "DIDP is not mutagenic *in vitro* in bacterial mutation assays (with and without metabolic activation) and is negative in a mouse lymphoma assay. It is not clastogenic in a mouse micronucleus assay *in vivo*. This suggests that DIDP is a non-genotoxic agent." DIDP tested negative in the L5178Y mouse lymphoma mutation assay and the Balb/3T3 cell transformation assay (*29*). The data from the mutation and cell transformation assay were reviewed by OECD.

The summary for Section 2, including general toxicity, toxicokinetics, and genetic toxicity, is located in Section 5.1.2.

3.0 DEVELOPMENTAL TOXICITY DATA

3.1 Human Data

There were no human data located for Expert Panel review.

3.2 Experimental Animal Toxicity

Three studies were found, two in rats and one in mice, that evaluated prenatal developmental toxicity following exposure by gavage to DIDP.

Hardin et al. (*30*) evaluated 60 chemicals, including 9 phthalates in the Chernoff-Kavlock assay in CD-1 mice. This is a screening protocol to prioritize chemicals for subsequent definitive developmental toxicity evaluations and to compare relative potencies. DIDP (CAS No. 26761-40-0) was administered by gavage on gestation day (gd) 6–13 at 0 or 9,650 mg/kg bw/day (undiluted chemical, 10 mL/kg bw/day) to 50 mice/group. The dams delivered their litters, and dams and pups were terminated on postnatal day (pnd) 3. There was no maternal mortality; there were no weight change effects and no effects on numbers of live litters, litter size, litter survival, birth weight, or weight gain.

Waterman et al. (Table WEB-1) (*31*) administered DIDP (CAS No. 68515-49-1) to 25 Sprague-Dawley rats/group on gd 6–15 by gavage at 0, 100, 500, and 1,000 mg/kg bw/day. The dams were sacrificed on gd 21 and implantation sites were evaluated. Fetuses were weighed and examined for external, visceral, and skeletal malformations. At 1,000 mg/kg bw/day, maternal toxicity was indicated by decreased weight gain and food consumption. Effects on fetal mortality or weight were not observed at any dose. Signs of developmental toxicity were seen in fetuses from dams that received 500 and 1,000 mg/kg bw/day. There was a statistically significant increase in the percent litters with 7th cervical ribs at the 1,000 mg/kg bw/day dose; a numerical increase in litter incidence with increasing dose (8.0, 18.2, 25, 41.7%) was also observed. A dose-related increase in the percent fetuses with a 7th cervical rib was observed, with the incidence at the two highest doses attaining statistical significance (1.0, 2.3, 6.2, 9.2%). A second skeletal variant, rudimentary lumbar (14th) rib(s), showed increased incidence at the two highest doses that was significant

on a percent litter basis at the highest dose and on a percent fetus basis at the two highest doses. Litter incidence values were 40.0, 36.4, 62.5, and 95.8%, while fetal incidence was 8.2, 9.0, 21.2, and 52%. Waterman et al. (*31*) interpreted their results as indicating a LOAEL for maternal and developmental toxicity at 1,000 mg/kg bw/day and a NOAEL of 500 mg/kg bw/day. The Expert Panel concurred with the maternal NOAEL but selected a developmental NOAEL of 100 mg/kg bw/day based on the significant incidence of cervical and accessory 14th ribs. The Expert Panel informed the sponsor of the Waterman et al. study that the Panel believed that there were more recent and superior methods for the analysis of pup incidence. The sponsor statistically reanalyzed findings of toxicological interest using the generalized estimating equation (GEE) approach to the linearized model (*32*) and shared its reanalysis results with the Panel (*33*). This is a pup-level analysis within a model that uses the GEE approach to account for the litter effect, i.e., the correlation between outcomes measured on pups within the same litter. The dose groups were tested pair-wise versus controls; this gave similar results to a trend test based on a dose-response model fit with all dose levels up to that of interest included. The results, presented in tabular form below, are consistent with the interpretation of the Expert Panel.

The sponsor also provided benchmark doses at the 5 and 10% excess risk level, based on a multiplicative (or 'extra') excess risk function. At the 5% excess risk level, the benchmark doses (and their 95% lower confidence limits estimated by bootstrap methods) were estimated as 188 (169), 258 (238), and 645 (515) mg/kg bw/day for rudimentary lumbar ribs, skeletal variants, and supernumerary cervical ribs, respectively.

Table 3: Mean Percent of Pups in Litter with Effect of Interest (significance level)

	Dose Group (DIDP mg/kg bw/day)			
	0	100	500	1,000
Skeletal Variations	19.8	20.6 (0.70)	31.9* (0.05)	64.1** (0.001)
Rudimentary Lumbar Ribs	8.4	9.4 (0.70)	21.9** (0.01)	51.9** (0.001)
Supernumerary Cervical Ribs	1.1	3.1 (0.28)	6.2* (0.03)	10.2** (0.004)

* $p \leq 0.05$, ** $p \leq 0.01$

Hellwig et al. (*34*) investigated the comparative developmental toxicity of a number of phthalates. They administered DIDP (CAS No. 26761-40-0) by gavage in olive oil at 0, 40, 200, and 1,000 mg/kg bw/day to Wistar rats on gd 6–15 in 7–10 pregnant rats per group (Table WEB 2). The dams were sacrificed on gd 20 and implantation sites were evaluated. Fetuses were weighed and examined for external, visceral, and skeletal malformations. At 1,000 mg/kg bw/day, there was maternal toxicity expressed as reduced feed consumption, vaginal hemorrhage in 3 dams, and increased absolute and relative liver weights. Kidney weight was unaffected. Developmental effects included increased incidences of percent fetal variations per litter (24.3, 37.2, 38.4, and 44.2% at 0, 40, 200, and 1,000 mg/kg bw/day, respectively) with the values at 200 and 1,000 identified as statistically significant. In the high-dose group, there were clear increases in rudimentary cervical ribs and accessory 14th ribs. An increased incidence of dilated renal pelves and hydroureter was observed at all treatment levels which apparently contributed to a statistically significant increase in the mean percent of fetuses affected per litter with variations at the 200 and 1,000 mg/kg bw/day doses. The data at 200 mg/kg bw/day are at odds with the authors' statement that "no substance-related effects were observed on dams, gestational parameters or fetuses among the two lower dose groups." Since there were increased incidences of total fetal variations at both 200 and 1,000 mg/kg bw/day, the Expert Panel concluded that 40 mg/kg bw/day was the developmental NOAEL and 200 mg/kg bw/day the maternal

NOAEL. The factors that led to the selection of these values, which differ from those of the authors, are discussed in Section 5.1.3.

Developmental effects were also observed in one- and two-generation reproductive toxicity studies in rats that are discussed in full detail under Section 4 (*35, 36*) (Table WEB-3). In both studies, dams were exposed to DIDP through diet from 10 weeks prior to mating through gestation and lactation. Dietary dose levels were 0, 0.25, 0.5, 0.75, and 1% for the one-generation study and 0, 0.2, 0.4, and 0.8% for the two-generation study. In the one-generation study, fetal body weights were lower in groups exposed to 0.5% DIDP and higher. There was no effect on offspring survival. For the two-generation study, developmental effects in F_1 offspring included a decrease in live pups at birth and on pnd 4 and a decrease in pup birth weight and weight gain in the high-dose group on pnd 0, 7, 14, and 21 for both sexes and also on pnd 4 for males. In F_1 pups, relative liver weights were significantly increased in females in the mid- and high-dose groups and males in the high-dose group. Liver cell hypertrophy and eosinophilia were also observed in the mid- and high-dose groups. F_1 females in the mid- and high-dose groups experienced a delay in vaginal opening (33.5 and 34.2 days, respectively, vs 32.2 days in control). The age of preputial separation was not affected in males, but the frequency of evaluation was not sufficient to rule out an effect. Developmental effects in F_2 pups were similar to those observed in F_1 pups. F_2 pup survival was reduced on pnd 1 and 4 in all treated groups, and also on pnd 7 and at weaning in the high-dose group. An unusually high incidence of pup deaths in 4, 2, and 4 litters of the low-, mid-, and high-dose groups respectively was noted; it was opined that reduced survival is usually observed in small numbers of pups distributed over many litters. F_2 pup birth weight was reduced in males of the high-dose group and postnatal weight gain was reduced in all pups of the high dose-group on pnd 1, 4, 7, 14, and 21. Four high-dose male pups had undescended testes, an effect that was probably related to delayed development. Although F_2 pup liver weight was not increased, liver cell hypertrophy and eosinophilia were observed in mid- and high-dose males and females. Because postnatal survival was reduced in all treated F_2 pups, a NOAEL was not identified for this study. The 0.2% dose (131–152 mg/kg bw/day and 162–379 mg/kg bw/day in F_0 and F_1 dams during gestation and lactation, respectively) was identified as the developmental LOAEL.

The two generation study was repeated by ExxonMobil Biomedical (*36*) using lower doses of 0, 0.02,0.06, 0.2, and 0.4% in feed (Table WEB-4). In addition to lower doses, this study incorporated measurement of anogenital distance on day of birth and assessment of nipple retention on pnd 13 or 14, on all offspring of both generations. Age at which vaginal patency and preputial separation occurred was noted for 2 rats/sex/dose for both F_1 and F_2 offspring. Dams were exposed for 10 weeks prior to mating throughout pregnancy and gestation. Complete details of the study, including a description of reproductive effects in parents and offspring, are included in Section 4. In the F_1 offspring there were no effects on pup survival, body weight, or organ weights. However, an increased incidence of dilated renal pelves (8/29 vs 0/30) were noted in adult F_1 males of the high-dose group (0.4%). The authors did not consider the effect to be biologically significant. Developmental results in F_2 offspring were consistent with findings of the previous 2-generation study (*35*). Effects at the 0.2% dose level included significant reductions in F_2 pup survival on pnd 1 and 4 and significant decreases in body weights of female F_2 pups on pnd 14 and male pups on pnd 35. At the 0.4% dose level, F_2 pup survival was significantly decreased on pnd 1 and 4 and body weights were significantly lower for female F_2 pups on pnd 14 and 21 and for males F_2 pups on pnd 14, 28, and 35. At the high dose, the liver to body weight ratio was increased in F_2 female pups sacrificed on pnd 21, but authors stated that the result was not biologically significant due to a lack of absolute organ weight change. A histological examination was not conducted. No treated F_1 and F_2 pups experienced differences from controls in either anogenital distance or abnormal nipple retention. A developmental NOAEL of 0.06% (38–44 and 52–114 mg/kg bw/day during pregnancy and lactation, respectively) was identified by the study authors.

In order to determine if postnatal developmental effects in pups are due to lactational transfer of DIDP, a cross-fostering and switched-diet experiment was conducted by Exxon Biomedical Sciences (*35*). For the

experiments, 20 CRl:CDBR VAF Plus rats/group were fed diets with 0 or 0.8% DIDP for 10 weeks prior to mating throughout the gestation and lactation periods. Approximate doses received by the dams for the premating, gestation, and lactation periods were 508–775, 524–551, and 641–1,582 mg/kg bw/day, respectively. For the cross-fostering portion of the study, the pups from ten treated dams were switched with pups from ten control dams. Nursing continued until weaning and the pups were then fed diets consistent with their lactational exposure for 10 weeks. For the switched-diet study, pups from control dams were fed the high-dose diet following weaning, and pups from treated dams were fed control diets after weaning for 10 weeks. Body weights were measured in both experiments.

Pups that were not exposed to DIDP *in utero*, but were nursed by treated dams, had lower body weights on pnd 14 and 21 than did controls (not exposed to DIDP during any portion of the study). The body weights of the pups remained lower (7–11%) during the 10-week period that they were fed DIDP-treated diets. Absolute and relative right testes weights and absolute left testes weights were reduced in these pups, but a histological examination was not conducted. No changes in body weights were noted for pups that were exposed to DIDP *in utero* but were then fostered by unexposed dams. In the switched-diet experiment, pups exposed to DIDP during gestation and lactation began to recover body weight and display normal growth patterns once they began to receive control diets at weaning. A slight decrease in body weight gain was observed in pups that were not exposed to DIDP during gestation and lactation but were fed DIDP-treated diets at weaning.

The summary for Section 3 is located in Section 5.1.3.

4.0 REPRODUCTIVE TOXICITY

4.1 Human Data

There were no human data located for Expert Panel review.

4.2 Experimental Animal Toxicity

Exxon Biomedical (*35*) conducted a one-generation reproductive range finding assay in rats. The rats were fed diets containing 0, 0.25, 0.5, 0.75, and 1% DIDP. There were no effects on reproductive indices. Toxicity in parents was limited to reduced body weight gain and/or reduced food intake in the 0.75 and 1% dose groups. Based on the results of the range finding assays, doses were selected for a two-generation study.

For the two-generation reproductive study, 30 Crl:CDBR VAF Plus rats/sex/group were fed diets containing 0, 0.2, 0.4, and 0.8% DIDP for 10 weeks prior to mating and during the mating period (*35*) (Table WEB-3). Treatment of the females continued through gestation and lactation. Author-estimated doses for the premating period were 103–198, 211–405, and 427–781 mg/kg bw/day for males and 127–203, 253–416, and 508–775 mg/kg bw/day for females. Doses received by females during the gestation and lactation periods were estimated at 131–149, 262–287, and 524–551 mg/kg bw/day and 172–361, 359–734, and 641–1582 mg/kg bw/day, respectively. Body weight and food intake were recorded weekly and estrous cycles were evaluated. Parental males were killed after mating and females were killed at weaning. A histological

examination was conducted for reproductive and other key organs (testes fixed in Bouin's). Primordial oocytes were counted in control and high-dose females. Sperm count, morphology, and motility were evaluated in males. F_1 pups were selected for mating at weaning and were fed diets with the same DIDP concentration as parental rats. Estimated doses for the F_1 rats were 117–216, 229–437, and 494–929 mg/kg bw/day in males and 135–218, 273–433, and 566–927 mg/kg bw/day in females during the premating period. Estimated dose levels for F_1 females during gestation and lactation were 135–152, 262–297, and 574–611 mg/kg bw/day and 162–379, 334–761, and 637–1,424 mg/kg bw/day, respectively. Vaginal opening and preputial separation were examined only in F_1 pups that were selected for mating. All other details for the F_1 mating experiment were the same as those for the first generation study.

Similar systemic effects were observed in the F_0 and F_1 adults. Weight gain and food intake were reduced in high-dose F_0 and F_1 females during the lactation period. Kidney to body weight ratios were increased in all treated males and mid- and high-dose females of both generations. Liver to body weight ratios were increased in mid- and high-dose parental rats from both generations. Histological effects included dilated renal pelves in high-dose F_1 males and renal casts observed mostly in high-dose F_0 and F_1 males. In the liver, centrilobular or diffuse hypertrophy and eosinophilia were noted in all treated parental rats of both generations. Mucosal erosion was also observed in the stomach of the mid- and high-dose F_0 females. Thymus atrophy (possibly related to decreased weight gain) was observed in high-dose F_0 and F_1 females. The length of estrous cycles was reduced in F_0 females of the high-dose group. In F_0 males, there was a significant, but small and non-dose related, decrease (<1.4%) in normal sperm in all treated groups. However, in F_1 rats there were no effects on estrous cycle length or sperm morphology. There were no effects on F_0 and F_1 mating, fertility, fecundity, and gestational indices. There were no lesions in the reproductive organs of F_0 and F_1 males and females and no differences in primordial oocyte or sperm counts. The decrease in absolute uterine weight and absolute and relative ovary weight in high-dose F_0 females and increases in relative weights of epididymis in mid- and high-dose males and testes in high-dose males were considered incidental due to a lack of histological effects.

In F_1 rats, there were no adverse effects on mating, fertility, fecundity, and gestational indices. There were no lesions in the reproductive organs of males and females and no differences in primordial oocyte or sperm counts. Increases in relative weights of epididymis and seminal vesicles in mid- and high-dose F_1 males and testes in high-dose males were considered incidental due to a lack of histological effects.

Developmental effects including decreased pup weight gain in the one-generation study and decreased pup weight gain and increased pup mortality in the two-generation study are discussed in detail under Section 3.0.

In a second two-generation reproductive study, 30 Crl:CDBR VAF Plus rats/sex/group were fed diets containing 0, 0.02, 0.06, 0.2, and 0.4% DIDP for 10 weeks prior to mating and during the mating period (*36*) (Table WEB-4). Treatment of the females continued through gestation and lactation. Author-estimated doses for the premating period were 12–23, 33–68, 114–225, and 233–453 mg/kg bw/day for males and 14–21, 40–58, 139–202, and 274–406 mg/kg bw/day for females. Doses received by females during the gestation and lactation periods were estimated at 13–15, 39–43, 127–147, and 254–295 mg /kg bw/day and 19–37, 57–112, 178–377, and 356–744 mg/kg bw/day, respectively. Body weight and food intake were recorded weekly. Parental males were killed after mating and females were killed at weaning. F_1 pups were examined for survival and growth during the lactation period. On pnd 4 litters were culled to four rats/sex. One F_1 pup/sex/litter was killed and necropsied on pnd 21. Another F_1 pup/sex/litter was selected for mating and at weaning was fed a diet with the same DIDP concentration as parental rats. Estimated doses for the F_1 rats were 32, 94, 313, and 635 mg/kg bw/day in males and 32, 95, 313, and 645 mg/kg bw/day in females during the first 2 weeks post-weaning and 11–26, 33–76, 114–254, and 235–516 mg/kg bw/day in males, and 14–25, 41–77, 137–266, and 271–524 mg/kg bw/day in females during the premating period. Estimated

dose levels for F_1 females during gestation and lactation were 13–15, 38–44, 134–151, and 256–286 mg/kg bw/day and 19–40, 52–114, 166–352, and 356–747 mg/kg bw/day, respectively.

The only systemic effects observed in F_0 and F_1 adults were increases in liver and kidney weights at the two highest doses as illustrated in Table WEB-4. In both generations of parental rats, there were no effects on mating, fertility, fecundity, or gestational indices at any dose level. F_1 and F_2 pups did not experience differences in the age of vaginal opening. The age of preputial separation was similar to controls in all F_1 pups but increased by 1.2 days in the high-dose F_2 pups; this modest change was not considered biologically significant by the authors. A fertility NOAEL of 0.4% (233–635 [M] and 271–645 [F] mg/kg bw/day) was selected by the authors.

Developmental effects including decreased pup weight gain and increased mortality were observed and are discussed in detail under Section 3.0.

Mode of Action

The estrogenic activity of DIDP has been examined using a battery of short-term *in vitro* and *in vivo* assays. Several studies have examined the ability of selected phthalate esters to compete with labeled estradiol (E2) for binding to the estrogen receptor (ER). Sources of ER protein included rat uterine cytosol (*37*), rainbow trout hepatic cytosol (*38*), recombinant human ERs (rhER) overexpressed in SF9 insect cells using the baculovirus system (*39, 40*) and rainbow trout ERs expressed in yeast (*41*). Triated E2 was used in the tissue cytosol binding assays while a high affinity fluorescent E2 derivative was used in the rhER binding assays. Selected phthalate esters have been examined in a number of in vitro gene expression assays systems. The assays have used stably transfected cells (*37*), transiently transfected cells (*37, 38*), yeast based assays (*37, 41-43*) and vitellogenin induction in rainbow trout hepatocyte cultures (*41*). DIDP did not compete with tritiated estradiol for binding to the rat uterine cytosolic estrogen receptor and did not induce the transcription of estrogen dependent genes (*37, 43*). DIDP, in contrast to the positive control estradiol, did not significantly induce an *in vivo* vaginal cornification response or increase in uterine weight at any of the concentrations tested (20, 200, and 2,000 mg/kg bw/day) over the course of a 5-day experiment using immature and adult ovariectomized Sprague Dawley rats (*37*). The lack of nipple retention and a normal anogenital distance in male offspring of rats exposed to DIDP at up to 295 mg/kg bw/day during gestation suggests a lack of antiandrogenic activity at that dose (*36*).

The summary for Section 4 is located in Section 5.1.4.

5.0 DATA SUMMARY & INTEGRATION

5.1 Summary

5.1.1 Human Exposure

DIDP, a complex substance of branched, predominantly C-10 isomers, is a general-purpose plasticizer for flexible PVC with a broad range of applications. It is widely used in construction and in general consumer product markets. Uses that result in general population exposure include artificial leather (shoes, gloves, clothing) and pool linings. DIDP is also used in children's vinyl toys. It has limited use in food packaging and is not used for medical applications (*1*).

There are no regulatory occupational limits, but manufacturers are reported to recommend 5mg/m^3, the ACGIH value for DEHP (*1*). Environmental monitoring data are scant. However, the monitoring data for DIDP in air, drinking water, and surface and ground waters have usually yielded negative results (i.e., concentrations below detection limits). In the few studies of food and infant formula, the levels of DIDP have been at or below the detection limit (0.01–0.1 mg/kg). Exposure through mouthing of toys is a unique circumstance. While no *in vitro* or *in vivo* data on DIDP leaching from toys are available, it is reasonable to postulate exposures several-fold higher than the general population in infants and toddlers who mouth DIDP-containing products. By analogy to DINP estimates, these exposures may be an order of magnitude higher for infants and young toddlers than exposures to older children and adults.

5.1.1.1 Utility of Data to the CERHR Evaluation

The Expert Panel believes it is reasonable to assume, based on the physicochemical characteristics of DIDP and existing, though limited, monitoring data, that the general population exposure level to DIDP is lower than to DEHP, which is estimated at 3–30 μg/kg bw/day (*10*). Exposure in children could represent an important exception to the propriety of extrapolating DIDP exposures from DEHP data. Potential unique exposures from mouthing toys and other objects that may contain DIDP permit only modest confidence in the adequacy of using DEHP estimates for estimating DIDP exposure in infants and toddlers.

5.1.2 General Biological and Toxicological Data

General Toxicity. Human data were not found for the categories presented in this section.

General toxicity studies for DIDP consist of a 21-day dietary study in rats, two 4-week dietary studies in rats, two 90-day dietary studies in rats, a 90-day dietary study in dogs, and a 2-week inhalation study in rats. The NOAELs, LOAELs, and effects from the feeding studies are listed in Table 4. Young adult rats (6 weeks old) were used in the 21- and 28-day feeding studies conducted by BIBRA (*11, 12*). The ages of rats in the other studies were not given, but body weights indicate they were equivalent to young adults. Animal age and weight were not available for the BASF rat studies. With the exception of one 28-day study in rats (*13*), histological examinations of testes were conducted. As noted, testicular histology was unaffected at doses up to 2,100, 1,287, and 586 mg/kg bw/day in the 21-day, 28-day, and 90-day studies, respectively. Increases in liver weight were consistently observed in all studies. The increases in liver weight were accompanied by biochemical evidence of peroxisomal proliferation at doses of 304 and 353 mg/kg bw/day in the 21-day and 28-day studies, respectively, conducted by BIBRA (*11*) and Lake (*12*). Additional liver effects that were reported in the 21-day rat study (*11*) included change in serum triglycerides and cholesterol and a change in hepatocyte cytoplasm staining properties. Increases in kidney weight and thyroid activity (as indicated by histological observations of follicle size, colloid, and epithelium) were only reported in the 90-day feeding study in rats at a dose of 586(M)–686(F) mg/kg bw/day.

General systemic effects were also studied in young adult dogs fed diets with up to 307(M)–320(F) mg/kg bw/day for 90 days. Hepatocellular swelling and vacuolization was observed in dogs at 77–320 mg/kg bw/day; effects were not observed at 15 mg/kg bw/day. Lesions were not observed in testes.

In an inhalation study, rats (ages not specified) were exposed to 505 mg/m^3 DIDP for 2 weeks (*17*). There were no systemic effects observed and toxicity was limited to local inflammatory changes in the lung.

The liver was identified as a target organ due findings in rats and dogs that were qualitatively consistent (e.g., increases in liver weight and the observance of vacuolated hepatocytes). As noted in Table 4, the NOAELs are fairly consistent for all dietary rat studies (116–264 mg/kg bw/day).

Table 4. Summary of NOAELs and LOAELs and Major Effects in General Toxicity Studies

Protocol and DIDP Doses (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day) and Effects	Major effects at higher doses
21-day repeat-dose dietary study in Fischer 344 rats. 6 weeks old at start of study, 5 rats/sex/group. Doses – M: 0, 304, 1,134, 2,100; F: 0, 264, 1,042, 1,972 (*11*)	M: None F: 264	M: 304; F: 1042 ↑ Liver weight. Peroxisomal proliferation. Basophilic liver changes (F).	↑ Liver weight. Peroxisomal proliferation. ↓Serum triglycerides and cholesterol. Basophilic and eosinophilic liver changes. **No** testicular lesions.
28-day repeat-dose dietary study in Fischer 344 rat. 6 weeks old at start of study, 5 male rats/group. Doses - 0, 25, 57, 116, 353, 1,287 (*12*)	116	353 ↑ Liver weight. Peroxisomal proliferation.	↑ Liver weight. Peroxisomal proliferation. **No** testicular lesions.
28-day repeat dose dietary study in Sprague-Dawley Rats. Age not known, 20/sex/group. Doses - M: 0, 600, 1,250; F:1,100, 21,00 (*13*)	None	M: 600; F: 1,100 ↑ Liver weight.	↑ Liver weight.
90-day repeat dose dietary study in Sprague-Dawley rats. Age not known, 20/sex/group. Doses - M: 0, 55, 100, 200, 400 F: 0, 60, 120, 250, 500 (*14*)	M: 200 F: 120	M: 400 ; F: 250 ↑Liver weight. ↓Weight gain in males.	↑Liver weight. ↓Weight gain in males. **No** testicular or ovarian lesions.
90-day repeat dose dietary study in Charles river CD rats Assume young adult based on body weight, 10/sex/group. Doses - M: 0, 28, 170, 586 F: 0, 35, 211, 686 (*15*)	M: 170 F: 211	M: 586; F: 686 ↑Liver weight. ↑Kidney weight (M). ↑Thyroid activity (slight histologic evidence). **No** testicular lesions.	No higher doses.
90-day repeat dose dietary study in young adult dogs, 3/sex/group. Doses - M: 0, 15, 77, 307 F: 0, 16, 88, 320 (*16*)	Sample size inadequate for evaluation of NOAEL	M: 77; F: 88 ↑ Liver weight, histological effects.	↓ Body weight. ↑ Liver weight, histological effects. **No** testicular lesions.

Toxicokinetics. DIDP administered orally to adult male rats is rapidly but incompletely absorbed (~56% at a dose of 0.1 mg/kg bw) and rapidly excreted via urine and feces with no accumulation in tissues (*22*). There was evidence of dose-limited absorption since ~46 and ~17% were absorbed after doses of 11 and 1,000 mg/kg bw, respectively. The data suggest partial saturation of the metabolism of DIDP to the

monoester in rat intestines within the dose range administered in the study (0.1–1,000 mg/kg bw). Saturation of intestinal esterase and pancreatic lipase may result in absorption of some unmetabolized parent compound, but no DIDP was detected, suggesting that most of the parent compound was excreted in the feces. Distribution to tissues was proportional to absorbed dose, suggesting that accumulation is not a factor. The major metabolites are the monoester and its side-chain oxidation products as well as phthalic acid. Dermal uptake over a 7-day period was quite low (~2%) in the rat (*18, 19*). *In vitro* studies with DEHP using human and rat skin (*44*) revealed that absorption was slower through human skin. Thus, it is reasonable to assume that dermal absorption of DIDP in humans would not be greater than that seen in rat dermal studies. Inhalation exposure of adult male Sprague Dawley rats to a single 6-hour dose of 91 mg/m^3 revealed initial high concentrations in lung with 27% of the concentration (radioactivity) still present after 72 hours. Distribution to other tissues was followed by rapid excretion via urine and feces (*17*).

Genetic Toxicity. OECD (*28*) recently concluded that DIDP is a non-genotoxic agent based on negative results in bacterial mutation assays, a mouse lymphoma assay, and a mouse micronucleus assay. In a subsequent publication negative results were obtained in the mouse lymphoma mutation and cell transformation assays conducted by Barber (*29*).

5.1.2.1 Utility of Data to the CERHR Evaluation

The oral subchronic studies in rat and dog are adequate for the evaluation of general toxicity induced by DIDP and indicate that the liver is a target organ. Some studies were conducted according to GLP standards and relevant exposure routes were utilized. Although sample sizes tended to be small in these studies, the results are generally consistent and reproducible, lending credence to the adequacy of the dataset. A modest concern is that rodent testes were preserved in formalin, which can lead to histopathological artifacts that may obscure subtle structural changes. However, reproductive organs in a two-generation rat study (discussed under Section 5.1.4) were preserved in Bouin's fixative and the histological observations observed were consistent with those from the general toxicity studies. Testes evaluation in the 90-day dog study was based on sections from Bouin's-fixed tissue. Peroxisomal proliferation was not examined in the 90-day exposure studies; however, it was present at 21 and 28 days in rat studies.

There is adequate general toxicokinetic data for DIDP, consisting of absorption, distribution, metabolism, and excretion, over a range of oral doses in the rat. There is also data on dermal and inhalation exposure in rats. While studies of toxicokinetics in humans have not been located, the DIDP toxicokinetic data in rats are consistent with the large body of data on phthalates that includes data on rodents and primates. It is reasonable to assume that the DIDP rodent data is relevant to humans.

5.1.3 Developmental Toxicity

Human data were not located for Expert Panel review.

Two published prenatal developmental toxicity studies in rats were available for DIDP (*31, 34*). The protocols for the 2 studies were similar and included dosing of dams by gavage on gd 6–15 with sacrifice and evaluation of fetuses on gd 20–21, although the group sizes differed. Developmental toxicity was also evaluated in a one-generation and in 2 two-generation toxicity studies (*35, 36*). The effects on pups from these studies are discussed below and summarized in Table 5; the reproductive effects from the one-generation and two-generation studies are described in Section 5.1.4.

Hellwig et al. (*34*) tested DIDP (CAS no. 26761-40-0) in Wistar rats (10/group) at doses of 0, 40, 200, and 1,000 mg/kg bw/day. Maternal toxicity was observed at the 1,000 mg/kg bw/day group and included

increased liver weights and vaginal hemorrhage. Fetal variations per litter were increased in the 200 and 1,000 mg/kg bw/day dose groups. These included increased rudimentary cervical ribs and increased accessory 14th ribs at 1,000 mg/kg bw/day; specific types of variations were not reported for the 200 mg/kg bw/day group. Hellwig et al. (*34*) reported "no substance-related effects" in dams or fetuses at doses up to 200 mg/kg bw/day, the middle dose tested. The Expert Panel did not find that the data supported a developmental NOAEL at 200 mg/kg bw/day given the reported statistically significant increase in total fetal variations at this dose, and agreed that the NOAEL is 40 mg/kg bw/day.

Of the two prenatal toxicity studies reviewed by the Expert Panel, Waterman et al. (*31*) was more informative due to the number of animals per test group (n=25) and completeness of data reported. Waterman et al. (*31*) tested DIDP (CAS no. 68515-49-1) in Sprague-Dawley rats (25/group) at doses of 0, 100, 500, or 1,000 mg/kg bw/day. Maternal toxicity at the highest dose consisted of decreased food consumption and weight gain. The effects on the offspring were presented as percent affected fetuses and percent affected litters. The percent fetuses with rudimentary cervical ribs was significantly increased at the two highest doses with a dose-related increase in litter incidence significant at the highest dose. There was a similar pattern of effect for accessory 14th ribs. Waterman et al. (*31*) interpreted their results as indicating a LOAEL for maternal and developmental toxicity at 1,000 mg/kg bw/day and a NOAEL of 500 mg/kg bw/day. The Expert Panel concurred with the maternal NOAEL but selected a developmental NOAEL of 100 mg/kg bw/day based on the significant incidence of cervical and accessory 14th ribs. A reanalysis of these Waterman et al. data by the study sponsor (see Section 3.2), using the GEE approach to the linearized model (*32*), provided results that are consistent with the Expert Panel interpretation.

The sponsor also provided benchmark doses at the 5 and 10% excess risk level, based on a multiplicative (or 'extra') excess risk function. At the 5% excess risk level, the benchmark doses (and their 95% lower confidence limits estimated by bootstrap methods) were estimated as 188 (169), 258 (238), and 645 (515) mg/kg bw/day for rudimentary lumbar ribs, skeletal variants, and supernumerary cervical ribs, respectively.

The Expert Panel noted that developmental toxicity was observed in the two rat studies where there was prenatal exposure and pups were examined just prior to birth. Developmental toxicity was also observed in both generations of the two-generation study in rats discussed below. In both prenatal studies, the skeletal system was the target for effects causing an increased incidence of cervical ribs and accessory 14th (lumbar) ribs. While effects at both sites are relevant to an assessment of development, the effect on cervical ribs is of greater toxicological concern. Cervical ribs are seen infrequently in controls, but more importantly, their presence may indicate a disruption of gene expression. In addition, some scientists express concern that cervical ribs may interfere with normal nerve function and blood flow. Rib responses were identical at the common dose of 1,000 mg/kg bw/day in the 2 studies. In the study where there was a larger group size (n=25), the litter incidence at this dose for each effect (cervical and lumbar) achieved statistical significance. In this same study, when incidence was expressed on a percent fetus basis (the proper term for analysis—percent affected fetuses per litter—was not reported) statistical significance was observed for each effect at the two highest doses. A numeric trend of increased incidence with increased dose was seen at all doses. In the study with fewer maternal rats per dose group (n=7–10), an increase in the incidence of hydroureter and of dilated renal pelves occurred in all treatment groups. This effect is at least indicative of a delay in maturation and while not clear in the publication, is thought to account partially for the reported increase in affected fetuses per litter with variation that achieved statistical significance at the two highest doses. The Panel further noted that this urinary tract effect occurred in the absence of reduced fetal weight; the absence of reduced fetal weight, which is usually a corollary to the urinary tract effect, provides a rationale for assuming maturational delay. The Panel further notes that LOAELs of 500 and 200 mg/kg bw/day and NOAELs of 100 and 40 mg/kg bw/day from these studies are reasonably consistent, the differences most likely reflect differences in dose selection between the two studies. Finally, it is noted that LOAELs for developmental toxicity occur at doses at which there were no demonstrable maternal effects.

Developmental effects were also observed in 2 two-generation reproductive toxicity studies. Details of the study procedures are addressed in Section 5.1.4. In the first study, rats were fed diets with 0, 0.2, 0.4, or 0.8% DIDP for 10 weeks prior to mating and throughout gestation and lactation (*35*). Hepatic hypertrophy and eosinophilia were observed in F_1 and F_2 male and female pups in the mid- and high-dose groups. Postnatal body weight gains were reduced in high-dose F_1 pups (pnd 0, 7, 14, and 21 for both sexes and pnd 4 for males) and F_2 pups (pnd 1, 4, 7, 14, and 21 for both sexes and pnd 0 for males). A reduction in postnatal survival was observed in F_1 pups of the high-dose group on pnd 0 and 4. In F_2 pups, postnatal survival was reduced on pnd 1 and 4 in all treatment groups and also on pnd 7 and 21 in the high-dose group. This increase in pup mortality was not observed in the one-generation range-finding study, but pup body weights were reduced in the three highest dose groups (*35*). Because a NOAEL could not be identified due to increased pup mortality in all dose groups, the study was repeated with lower doses of 0, 0.02, 0.06, 0.2, and 0.4% DIDP in the diet (*36*). No developmental effects were observed in the F_1 pups. However, increased mortality was noted in the F_2 pups of the two highest dose groups on pnd 1 and 4. Reductions in pup body weight gain were also noted for F_2 pups in the 0.2% dose group (females on pnd 14 and males on pnd 35) and 0.4% dose group (females on pnd 14 and 21, and males on pnd 14, 28, and 35). Hormonally-mediated endpoints such as anogenital distance and nipple retention in males were not observed at doses up to 0.4% in diet. Maternal effects were limited to increased liver weight with mild histological effects.

Cross-fostering and switched-diet satellite studies with rats fed the 0.8% diet indicated that lactational exposure is a meaningful factor in the reduction of body weight gain in pups (*35*). The data are sufficient to conclude that DIDP, administered through diet, is a developmental toxicant in rats based on reduced fetal survival and body weight observed in two studies. A developmental NOAEL of 0.06% (38–44 and 52–114 mg/kg bw/day during pregnancy and lactation, respectively) was identified by the study authors.

A screening-design study in mice (*30*), where an oral gavage dose of 9,650 mg/kg bw/day was administered on gd 6–13, did not report any developmental or maternal toxicity through pnd 3. This study is insufficient to conclude that DIDP is not a developmental toxicant in mice since a full teratological examination was not performed. It does indicate that a dose almost 10-fold greater than that which caused effects in rats does not affect pregnancy outcome or early postnatal survival and growth in mice.

Table 5. Summaries of NOAELs and LOAELs and Major Effects in Developmental Toxicity Studies

Protocol & Study	NOAEL (mg/kg bw/day) [Benchmark dose – ED_{05} in mg/kg bw/day]	LOAEL (mg/kg bw/day)		Developmental Effects Observed at Higher Dose Levels
		Maternal	Developmental	
Prenatal gavage study in Wistar rats. 10/group received 0, 40, 200, or 1,000 mg/kg bw/day on gd 6–15. Dam and pups examined in late gestation. (*34*)	200 for maternal 40 for developmental***	1,000 ↑ Liver weights and vaginal hemorrhage.	200 ↑Variations. (No specific type of variation reported.)	↑Variations (cervical and lumbar ribs).

Prenatal gavage study in Sprague-Dawley rats. 25 per group received 0, 100, 500, or 1,000 mg/kg bw/day on gd 6–15. Dams & pups examined in late gestation. (*31*)	500 for maternal 100 for developmental*** [MLE(95%LCL): 258 (238) for skeletal variants, 188 (169) for lumbar ribs, 646 (515) for cervical ribs.]	1,000 ↓ Weight gain.	500 ↑ Fetuses with variations (lumbar and cervical ribs).	↑ Fetuses and litters with variations (lumbar and cervical ribs).
Two-generation reproductive dietary study in Crl:CDBR, VAF Plus rats. 30 dams/group were fed diets with 0, 0.2, 0.4, or 0.8% DIDP from 10 weeks prior to mating through gestation (131–152, 262–297, 524–611 mg/kg bw/day*) and lactation 162–379, 334–761, 637–1,582 *). (*35*)**	None for maternal or developmental	131–379 Hepatocyte enlargement.	131–379 ↓ Postnatal survival in F_2.	↓ Postnatal survival in F_1 and F_2. ↓Postnatal weight gain in F_1 and F_2.
Two generation reproductive dietary study in Crl:CDBR, VAF Plus rats. 30/group were fed diets with 0, 0.02, 0.06, 0.2, or 0.4% DIDP from 10 weeks prior to mating through gestation (13–15, 38–44, 127–151, or 254–295 mg/kg bw/day*) and lactation (19–40, 52–114, 166–377, 356–747*). (*36*)**	38–114 for Maternal and developmental	127–377 ↑ Liver weight.	127–377 ↓ Postnatal survival in F_2. ↓ Decreased weight gain in F_2.	↓ Postnatal survival in F_2. ↓ Decreased weight gain in F_2.
Prenatal gavage toxicity screening assay in CD-1 mice. 50 dams/group received 0 or 9,650 mg/kg bw/day on gd 6–13. Dams and pups evaluated on pnd 3 for litter size and survival and body weight changes only. (*30*)	9,650 for maternal and developmental. (Note – there was no examination of fetal variations or malformations.)	No higher doses.	No higher doses.	No higher doses.

* Combined doses for F_0 and F_1 dams during gestation and lactation.
** Only maternal and developmental effects were listed in this Table. Reproductive and male systemic effects are listed in Table 6.
*** NOAEL selected by Expert Panel is lower than study author's selection.

5.1.3.1 Utility of Data to the CERHR Evaluation

There are adequate data available in rats to determine that prenatal oral exposure to DIDP results in developmental toxicity. The results of the Waterman et al. (*31*) and the Hellwig et al. (*34*) studies were remarkably consistent and included increases in lumbar and cervical ribs. In addition, the effective dose levels were similar. The data from the 2 two-generation dietary studies are sufficient to demonstrate an effect on postnatal survival and growth.

5.1.4 Reproductive Toxicity

Human data were not located for Expert Panel review.

Structural and functional reproductive effects were examined in a one-generation (dose setting) and 2 two-generation studies in rats that included *in utero* exposure for the duration of pregnancy (*35, 36*). In the one-generation study, rats were administered dietary levels of 0, 0.25, 0.5, 0.75, and 1% DIDP. In the two-generation studies, rats were administered dietary levels of 0, 0.2, 0.4, and 0.8% DIDP or 0, 0.02, 0.06, 0.2, and 0.4% DIDP (*35, 36*). In the two-generation studies, there were no effects on F_0 or F_1 mating, fertility, fecundity, and gestational indices at doses up to 427–929 and 508–927 mg/kg bw/day in males and females, respectively. A small, non dose-related decrease in normal sperm (<1.4%) was seen in all treated F_0 males and a reduced length of estrous cycles occurred in F_0 females that received the highest dose, but those effects were not observed in the F_1 rats. There were no histologic lesions in the reproductive organs of F_0 or F_1 males and females and no differences in primordial oocyte or sperm counts. The lack of effects on reproductive function was consistent with effects observed in the one-generation range-finding study. In the two-generation reproductive toxicity study with higher doses, systemic effects in parental rats included hepatocyte hypertrophy at all dose levels, increased kidney weights in low-dose males and all mid- and high-dose animals, and dilated renal pelves and renal casts in high-dose males (*35*). Developmental effects included hepatic hypertrophy and reduced postnatal survival and are discussed in detail in Section 5.1.3. Parental systemic and developmental toxicity were similar to those described in the second two generation reproductive toxicity study (*36*).

DIDP did not appear to have effects on male reproductive tract development or function. An increase in seminal vesicle to body weight ratio in F_1 males of the 0.4% group and epididymis to body weight ratio in F_0 and F_1 males at the 0.4% dose was not considered adverse because reproductive function was unaffected and there were no histopathological effects (*35*). Thus, the highest dose of 0.8% (M: 427–929 mg/kg bw/day and F: 508–927 mg/kg bw/day) was identified as the NOAEL for reproductive toxicity.

Table 6. Summaries of NOAELs and LOAELs and Major Effects in Reproductive Toxicity Studies

Protocol & Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day) and Effects		Effects Observed at Higher Dose Levels
		Reproductive	Systemic	Reproductive
Two-generation reproductive dietary study in Crl:CDBR, VAF Plus rats. 30 rats/sex per group were fed diets with 0, 0.2, 0.4, or 0.8% DIDP (M: 0, 103–216, 211–437, 427–929 mg/kg bw/day; F: 0, 127–218, 253–433, 508–927 mg/kg bw/day*) from 10 weeks prior to mating through gestation and lactation. (*35*)**	Reproductive: M: 427–929 F: 508–927 Systemic: none	No effects on reproductive structure or function.	M: 103–216 F: 127–218 Hepatocyte enlargement. ↑ Kidney weights (M).	None
Two-generation reproductive dietary study in Crl:CDBR, VAF Plus rats. 30 rats/sex per group were fed diets with 0, 0.02, 0.06, 0.2, or 0.4% DIDP (M: 0, 11–32, 33–94, 114–313, or 233–635 mg/kg bw/day; F: 0, 14–32, 40–95, 137–313, or 271–645 mg/kg bw/day***) from 10 weeks prior to mating through gestation and lactation (*36*)**	Reproductive: M: 233–635 F: 271–645 Systemic: M: 33–94 F: 40–95	No effects on reproductive development, structure, or function.	M: 114–313 F: 137–313 ↑ Liver and kidney weights.	None

* Doses during the premating period – combined for F_0 and F_1 rats

** Only effects in parental rats and effects in the reproductive system are listed. Developmental effects are listed in Table 5.

*** Doses during the premating period and first 2 weeks postweaning for F_1 rats - combined for F_0 and F_1 rats.

Mode of Action

DIDP exhibited no activity in *in vitro* assays that measured binding of phthalates to rat uterine cytosolic estrogen receptors and in an assay of estrogen-induced gene expression (*37, 43*). The monoester of DIDP was not tested *in vitro*. *In vivo* assays demonstrated that DIDP does not increase uterine wet weight or vaginal epithelial cell cornification in immature or mature ovariectomized rats (*37*). The lack of nipple retention and a normal anogenital distance in male offspring of rats exposed to DIDP at up 295 mg/kg bw/day during gestation suggests a lack of antiandrogenic activity at that dose (*36*).

5.1.4.1 Utility of Data to the CERHR Evaluation

Data are sufficient to indicate that oral DIDP exposures are not associated with detectable effects on reproduction at doses up to 427–929 mg/kg bw/day in male and 508–927 mg/kg bw/day in female rats. Testicular lesions were not observed in histological examination of testes in dogs exposed to doses of 307 mg/kg bw/day in a 90-day study. The data from the two-generation studies were collected utilizing a protocol acceptable to the US, EU, and other OECD countries. They were performed in accordance with GLP requirements. Reproductive organs were preserved in Bouin's fixative, a method which reduces histological artifacts. One of the studies included an evaluation of hormonally-mediated postnatal effects that were found to be the most sensitive indicators of toxicity for other phthalates. Thus, the data provide a valuable database for evaluating reproductive toxicity potential in rats.

5.2 Integrated Evaluation

DIDP is a complex substance of branched, predominantly C-10 isomers. There are no human data from which to assess the health effects associated with DIDP exposure; studies of DIDP toxicity are limited to laboratory animals. In the absence of human data to the contrary, it is assumed that the effects observed in laboratory animals are relevant to humans.

Based upon the physicochemical similarities between DIDP and DEHP, and on limited DIDP monitoring data, general population exposure is expected to be lower than that of DEHP, which is estimated at 3–30 µg/kg bw/day. It is reasonable to presume that humans would be exposed primarily through the oral route. Although data are scant, the ingestion of DIDP through food does not appear to be common. Children may have higher levels of exposure to DIDP than adults because infants and small children mouth toys and other objects that may contain DIDP which can migrate into saliva and be swallowed. There is no use of DIDP in medical devices, therefore intravenous exposure does not occur.

Orally-administered DIDP is metabolized by intestinal luminal enzymes and the resulting metabolites are absorbed into the blood and further metabolized or conjugated and quickly excreted into urine or feces. Persistence or accumulation in the body is not expected. Toxicokinetic studies in rats have demonstrated that DIDP has limited dermal absorption and does not persist or accumulate in the body.

There are data available in rodents from which to evaluate developmental and reproductive effects associated with oral DIDP exposure. Developmental studies in rats include assessment of prenatal exposure on prenatal effects. Postnatal developmental effects following prenatal exposure have also been assessed using endpoints that have been adversely affected in studies with other phthalates. Two prenatal gavage exposure studies in rats with treatment of dams from gd 6–15 did not cause structural malformations but did consistently demonstrate developmental toxicity (increased fetal cervical and lumbar ribs) at doses of 200–500 mg/kg bw/day and higher. The more robust of the two studies was determined by the Expert Panel

to have a maternal NOAEL of 500 mg/kg bw/day and a developmental toxicity NOAEL of 100 mg/kg bw/day**,** while a second study determined a developmental NOAEL of 40 mg/kg bw/day. Developmental toxicity was observed and replicated in 2 two-generation reproductive dietary studies in rats where adverse effects on pup growth or survival were observed at gestational doses of 127–151 mg/kg bw/day and higher and a lactational dose of 166–377 mg/kg bw/day and higher; the developmental NOAEL is in the range of 38–44 mg/kg bw/day (gestational) and 52–114 mg/kg bw/day (lactational). A prenatal exposure-screening study in mice in which an oral gavage dose of 9,650 mg/kg bw/day was administered did not report any developmental or maternal toxicity. While insufficient to conclude that DIDP is not a developmental toxicant in mice, it does indicate that a dose that is almost 10-fold greater than that which caused effects in rats does not affect pregnancy outcome or early postnatal survival and growth in mice.

Reproductive performance and histological effects on sex organs were assessed. Parental doses of up to 0.8% in feed (~ 427–929 in males and 508–927 mg/kg bw/day in females) did not affect fertility or sex organ histology in either the parents or F_1 male or female pups. Sub-chronic studies (21–90 day exposure) gave no gross or histologic evidence of effects on testes at doses up to 2,100 mg/kg bw/day in rats and 307 mg/kg bw/day in dogs. These doses did produce liver hypertrophy, mild evidence of toxicity, and clear signs of peroxisome proliferation in rats. The Expert Panel notes that the liver was consistently identified as the target organ in general toxicity studies with adult rats and in developmental and multigeneration studies. Hepatic effects in offspring exposed *in utero* were principally associated with liver enlargement observed at weaning and in adults.

5.3 Expert Panel Conclusions

DIDP is used in construction and in general consumer products. DIDP was detected in older surveys of toys, but recent surveys have not detected DIDP in toys. In surveys of retail food samples, DIDP concentrations were below the detection limits. Although data are scant, exposure through food appears to be lower than for DEHP. Therefore, the Expert Panel believes that adult exposure to DIDP will not exceed levels of 3–30 μg/kg bw/day, the estimates derived for DEHP. Exposures to DIDP are likely to be below this level, but the Panel could not quantitate how far below. Occupational exposures could occur through inhalation and dermal contact. Limited studies of occupational exposures suggest that inhalation exposure is below 1 mg/m^3 during production of DIDP and below 2 mg/m^3 during production of PVC. Although estimates of dermal exposure are not available, the Expert Panel is confident that dermal exposure would not result in significant absorption into the body. Exposure of children to DIDP could also occur through contaminated food. However, DIDP has not been detected in surveys of infant formula.

The toxicology database is sufficient to determine that oral maternal exposure to DIDP can result in developmental toxicity to the conceptus. In rats, two prenatal developmental studies have shown effects on the developing skeletal system following oral exposure to DIDP. The NOAEL for these studies was 40–100 mg/kg bw/day. In addition, developmental toxicity was noted in two oral two-generation reproductive toxicity studies in rats. Both studies showed effects on pup survival and growth. These effects may be due to prenatal and/or lactational exposures to DIDP. The NOAELs for the studies were 38–44 mg/kg bw/day during pregnancy and 52–114 mg/kg bw/day during lactation. Based on the results of the toxicology studies, oral exposure to pregnant humans and oral exposure to children should be examined. To date, the only available oral exposure information is based on the conservative estimate derived for DEHP of 3–30 μg/kg bw/day. The Expert Panel has minimal concern for children and fetuses due to exposure to ambient levels of DIDP. The Expert Panel cannot judge the potential health effects in children from mouthing of objects containing DIDP due to the lack of exposure information. In addition, the Expert Panel cannot judge the potential hazards to unborn children following maternal occupational exposures due to the lack of toxicology data following inhalation exposures and the lack of occupational exposure information.

The oral prenatal developmental toxicity studies and the oral two-generation reproductive toxicity studies have shown no effects on the reproductive system in rats. The Expert Panel noted that the endpoints of reproductive development that have been shown to be sensitive with other phthalates were examined in one of the two-generation reproductive toxicity studies. The NOAEL for reproductive toxicity ranges from 427–929 mg/kg bw/day. Therefore, the Expert Panel has minimal concern about DIDP resulting in reproductive toxicity in humans.

5.4 Critical Data Needs

Critical data needs are discussed under two categories: experimental studies and human exposure.

Experimental Studies

The Expert Panel recommends a sequential approach for future studies that would focus on obtaining the most critical information first. Subsequent studies would be dependent upon the results of the initial study. The Panel further recognized that data gathering should be an iterative process and that the recommendations may change as initial tiers of data are gathered. The Expert Panel recommends that the following sequential steps be considered.

A perinatal developmental study by the oral route in a non-rodent species. There are species differences in the developmental toxicity associated with other phthalates. The developmental effects of DIDP have only been examined in the rat and in a mouse screening study. Therefore, there is some uncertainty whether other species would exhibit similar responses and whether the rat is an appropriate model for assessing potential human risk.

Human Exposure

1. Human exposure to DIDP has not been well studied; there are no reports of levels in biological materials (blood, urine, etc.), and the environmental data consist primarily of estimates.

2. Patterns of use, expected environmental levels, and vulnerability of exposed population groups should dictate decisions about measuring DIDP in environmental media. For example, determining DIDP exposures in young children is of highest priority, based on the use patterns and vulnerability described above. Workers producing PVC products are a second priority.

3. Collection of biological samples *de novo* should be accompanied by environmental measurements to provide information on exposure sources. Existing biological samples should be utilized where available if they can provide useful information about exposure.

4. Although information about exposure of young children is a critical data need, manufacturers of children's toys should be polled to determine if their products will continue to contain DIDP in the future. If so, an estimate of the DIDP content should be made by the manufacturer and confirmed by independent studies. Salivary extraction of DIDP itself is important in order to evaluate the exposure directly, and not by use of a proxy (DINP). Better estimates of mouthing behavior, especially within the potentially highest risk group of 3–12 months, using larger samples of children, are also needed. The initial assessment of DIDP in toys is particularly important because no DIDP was found in a US sample of 35 toys, and the UK studies of 1992 and 1996 reported the same negative result.

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7.0 WEB TABLES