Existing Chemical Hazard Assessment Report

Australian Government
Department of Health and Ageing
NICNAS

Diisodecyl Phthalate

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME
GPO Box 58, Sydney NSW 2001, Australia www.nicnas.gov.au

Preface

This report was compiled under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act), which came into operation on 17 July 1990.

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Overview

This review of diisodecyl phthalate (DIDP) is a health hazard assessment only. For this assessment, two key reviews on DIDP prepared by the European Chemicals Bureau (ECB) and the US Centre for the Evaluation of Risks to Human Reproduction (CERHR) were consulted. These reviews were supplemented with literature surveys conducted up to September 2006.

Structurally, phthalate esters are characterized by a diester structure consisting of a benzenedicarboxylic acid head group linked to two ester side chains. DIDP possesses 2 branched ester side chains each with a backbone of predominantly 10 carbons (C10).

DIDP is mainly used as a plasticiser for polyvinyl chloride (PVC). DIDP accounts for about one fifth of the total plasticisers used in Europe. DIDP plasticised PVC is used in film, sheet and coated products, flooring, roofing and wall coverings and car undercoating and sealants. Through extrusion and injection moulding processes it is also used for hose, wire and cable, footwear and miscellaneous articles. Non-PVC uses include polymers such as pressure sensitive adhesives, printing inks, anti-corrosion and anti-fouling paints. Current EU legislation restricts the use of DIDP in certain toys and childcare articles which can be placed in the mouth.

In Australia, DIDP is imported as finished products or mixtures, and as a raw chemical for local manufacture of products. The chemical is used industrially as a plasticiser for PVC in automotive parts, automotive and domestic vinyl, hoses, gaskets, cable and wire coatings. It is also used in non-vinyl applications such as adhesives and surfactants. Imported products containing DIDP include packaging materials, industrial flooring, paints, surfactants, flame resistant plastics, PVC films, children's toys and exercise balls.

Toxicity data for DIDP was not available for all health endpoints. For endpoints with missing or incomplete data, information from structurally similar phthalates, where available, was used to extrapolate potential toxicity. Relevant read-across information was obtained from other NICNAS hazard assessment reports for phthalates and the NICNAS Phthalates Hazard Compendium, which contains a comparative analysis of toxicity endpoints across 24 ortho-phthalates, including DIDP.

Following single oral gavage doses in rats, absorption of DIDP from the gastro intestinal tract was incomplete and decreased as the dose increased. In rats, dermal absorption was low (2-4%). Absorption of DIDP from the lung following inhalation exposure was approximately 73%. Following absorption, DIDP was rapidly eliminated via urine and faeces. The major metabolites detected in urine were phthalic acid and the oxidised monoester derivative, while the parent compound, the oxidised monoester derivative and MIDP were detected in faeces.

DIDP has low acute oral, dermal and inhalation toxicity. It is a mild skin and eye irritant. It is not considered a skin sensitiser.

In repeated dose oral studies with DIDP in rats, the main effects at 120 mg/kg bw/d and above were increased liver weights and lipid metabolism in the liver in the absence of associated pathology. The NOAEL was 60 mg/kg bw/d. In a repeated dose toxicity study of limited reliability in dogs, which is considered a more relevant species to humans with respect to peroxisome proliferation, a LOAEL of 75 mg/kd bw/d was reported for increased liver weights and histological changes. The NOAEL was 15 mg/kg bw/d. Current literature

indicates that rodents compared to humans are particularly susceptible to peroxisome proliferative effects. In the light of peroxisome proliferative effects observed for DIDP, liver effects from DIDP exposure may not be relevant for humans.

DIDP was considered not to be genotoxic, based on the results collected from in vitro bacterial mutation assays, in vitro mouse lymphoma assays and an in vivo mouse micronucleus assay.

There were no in vivo carcinogenicity studies available for DIDP. One of two in vitro cell transformation assays was positive for transforming potential. The majority of phthalates have not been adequately tested for carcinogenicity and attempts to correlate carcinogenic potential of DIDP from similar phthalates is not possible.

In two 2-generation reproduction studies with rats, DIDP caused increased liver and kidney weights in parental animals and reduced pup survival, which was more pronounced in the F2 pup generation. There was no evidence to indicate that DIDP causes impairment of fertility. No testicular lesions were reported in repeat dose studies in rats at doses up to 2000 mg/kg bw/d. A NOAEL for fertility was determined at 0.8% (427-927 mg/kg bw/d).

In both two-generation studies, pup survival was reduced in the F2 generation. This may be a result of lactational exposure to DIDP. The LOAEL for pup survival was 0.2% (134-352 mg/kg bw/d). The NOAEL was 0.06% (38-114 mg/kg/d).

An increased incidence of foetal variations (rudimentary lumbar ribs and supernumerary cervical ribs) was seen in a rat developmental study. However, in the absence of more profound signs of developmental toxicity, findings of supernumerary ribs were generally considered minor and there were no biologically important findings at ≤ 500 mg. Therefore, a developmental NOAEL of 500 mg/kg bw/d on a per litter basis was determined based on increased skeletal variations at 1000 mg/kg bw/d.

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Acronyms And Abbreviations

bw	body weight
C	Celsius
CAS	Chemical Abstracts Service
CERHR*	Center for the Evaluation of Risks to Human Reproduction
DIDP	diisodecyl phthalate
d	day
f	female
F0	parental generation
F1	filial 1 (first generation)
F2	filial 2 (second generation)
g	gram
GD	gestation day
GIT	Gastro-intestinal tract
GLP	good laboratory practice
h	hour
kg	kilogram
kPa	kilopascals
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LOAEL	lowest-observed-adverse-effect level
m	male
m^3	cubed metre
mg	milligram
MIDP	monoisodecyl phthalate
mL	millilitre
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Cooperation and Development
P1	parental generation (first)
P2	parental generation (second)
PND	post-natal day

ppm	parts per million
PVC	polyvinyl chloride
w/w	weight per weight
µL	microlitre
µg	microgram

1. Introduction

This review of diisodecyl phthalate (DIDP) is a health hazard assessment only. For this assessment, two key reviews on DIDP prepared by the European Chemicals Bureau (ECB) and the US Centre for the Evaluation of Risks to Human Reproduction (CERHR) (both dated 2003) were consulted. These reviews were supplemented with literature surveys conducted up to September 2006.

Information on Australian uses was compiled from data supplied by industry in 2004 and 2006.

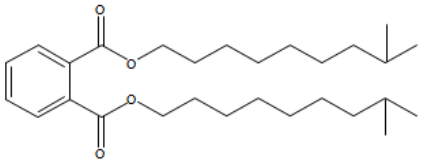
References not marked with an asterisk were examined for the purposes of this assessment. References not examined but quoted from these two reports as secondary citations are also noted in this assessment and marked with an asterisk.

Hazard information from this assessment is published also in the form of a hazard compendium providing a comparative analysis of key toxicity endpoints for 24 *ortho*-phthalate esters (NICNAS, 2008).

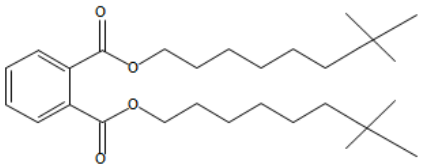
2. Identity

2.1 Identification of the substance

CAS Number:	68515-49-1 and 26761-40-0
Chemical Name:	1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters C10-rich (68515-49-1); 1,2-Benzenedicarboxylic acid, diisodecyl ester (26761-40-0)
Common Name:	Diisodecyl phthalate
Molecular Formula:	$C_{28}H_{46}O_4$ (average)
Structural Formula:	CAS Number 68515-49-1



CAS Number 26761-40-0



Molecular Weight:	447 (average)
Synonyms:	DIDP
Purity/Impurities/Additives:	Purity ≥ 99.5% w/w

Note: Chemically, the structure of DIDP is that illustrated above (CAS No. 26761-40-0). However, in the chemical industry, DIDP (CAS No. 68515-49-1) refers to a C-10-rich mixture containing C9-11 branched dialkyl phthalate esters. The tertiary butyl structure is one of the C10-rich components of this mixture.

2.2 Physico-chemical properties

Table 1: Summary of physico-chemical properties

Property	Value
Physical state	Oily viscous liquid
Melting point	-45ºC (average)
Boiling point	>400ºC
Density	970 kg/m^3 (20°C)
Vapour pressure	5.1 x 10^{-8} kPa (25°C)
Water solubility	2 x 10^{-7} g/L (20°C)
Partition coefficient n-octanol/water (log value)	8.8
Henry's law constant	114 Pa.m^3/mol
Flash point	>200ºC

Source: CERHR (2003), ECB (2003)

3. Uses

DIDP is mainly used as a plasticiser for polyvinyl chloride (PVC). DIDP accounts for about one fifth of the total plasticisers used in Europe. DIDP plasticised PVC is used in film, sheet and coated products, flooring, roofing and wall coverings and car undercoating and sealants. Through extrusion and injection moulding processes it is also used for hose, wire and cable, footwear and miscellaneous articles. Non-PVC uses include polymers such as pressure sensitive adhesives, printing inks and anti-corrosion and anti-fouling paints (ECB, 2003). Current EU legislation restricts the use of DIDP in certain toys and childcare articles which can be placed in the mouth.

In Australia, DIDP is imported as finished products or mixtures and as a raw chemical for local manufacture of products. The chemical is used industrially as a plasticiser for PVC in automotive parts, automotive and domestic vinyl, hoses, gaskets, cable and wire coatings. It is also used in non vinyl applications such as adhesives and surfactants. Imported products containing DIDP include packaging materials, industrial flooring, paints, surfactants, flame resistant plastics, PVC films, children's toys and exercise balls.

4. Human Health Hazard

4.1 Toxicokinetics

Previous evaluations

Oral

Following single oral gavage doses in rats of 0.1, 11.2 or 1000 mg/kg bw of ^{14}C-DIDP in corn oil, the amounts absorbed were estimated from the total radioactivity excreted in urine and bile or retained in the carcass after 72 hours (General Motors Research Laboratories, 1983*). Absorption of DIDP from the gastrointestinal tract (GIT) tract was incomplete and decreased as the dose increased (56, 46 and 17% for the low, medium and high doses, respectively). There was evidence of some enterohepatic recirculation.

Tissue residue levels of radioactivity were less than 1% at sacrifice on day 3 with 99% of the administered dose eliminated via urine and faeces, regardless of dose. The highest concentration of radioactivity was observed in the GIT, liver and kidney. The majority of the ^{14}C-DIDP dose was excreted in faeces (57, 65 and 81% for the low, medium and high dose, respectively) with around 41, 32 and 12% respectively excreted in the urine over the same period.

The major metabolites detected in urine were phthalic acid and the oxidised monoester derivative, while the parent compound, the oxidised monoester derivative and monoisodecyl phthalate (MIDP) were detected in faeces. High content of MIDP in the faeces is consistent with a proposed mechanism that de-esterification to the monoester form and an alcohol moiety occurs via non-specific pancreatic lipase and intestinal mucosa esterases prior to absorption.

Dermal

When ^{14}C-DIDP was applied to rat skin at 16.3 mg/cm^2 under occlusion, around 2-4% of the dose was absorbed after 7 days (Elsisi et al., 1989). A similar amount of dermal absorption was observed when DIDP was applied to rat skin at 5-8 mg/cm^2 (Midwest Research Institute, 1983*).

Inhalation

When rats were exposed to 100 mg/m^3 of an aerosol of ^{14}C-DIDP for 6 hours by inhalation (head only), absorption from the lung was about 73% (General Motors Research Laboratory, 1981*). Three days following administration, 27, 8, 9 and 10% of the dose was found in the lung, gut, liver and kidney, respectively. Excretion was via urinary and faecal routes (45 and 41% of the total dose, respectively).

Data not reported in previous evaluations

No data.

Conclusion

Animal studies show that following absorption DIDP is rapidly eliminated via urine and faeces and does not accumulate in tissues. In rats, less than 1% of a radioactive dose remained in tissues after 72 hours. Absorption of DIDP from the lungs in a single dose study was determined to be about 73%. Dermal absorption was observed to be very low (2-4%). Following single oral gavage doses in rats, absorption of DIDP from the GIT tract was incomplete and decreased as the dose increased. The major metabolites detected in urine were phthalic acid and the oxidised monoester derivative, while the parent compound, the oxidised monoester derivative and MIDP were detected in faeces.

4.2 Acute toxicity

Previous evaluations

Most of the animal studies considered were either not available as detailed studies or were performed prior to establishment of Good Laboratory Practice (GLP), OECD or EU Test Guidelines. Thus, details on the treatments often were not available. However, results for all routes of exposure were comparable. The results are summarised in Table 2.

Table 2: Acute animal toxicity studies

Study	Species	Results (LD50/LC50)	References
Oral	Rat	>62080 mg/kg bw	Smyth et al., 1962*
	Rat	>29100 mg/kg bw	BASF, 1961*
Dermal	Rat	>2910 mg/kg bw	Inveresk Research International, 1981*
	Rabbit	>3160 mg/kg bw	Industrial Bio-test Laboratory, 1975*
	Rabbit	>3160 mg/kg bw	Hazleton Laboratories America, 1978*
Inhalation (4-h)	Rat	>12540 mg/m^3	Inveresk Research International, 1981*

Data not reported in previous evaluations

No data.

Conclusion

DIDP has low acute toxicity with oral LD50 values of > 29100 mg/kg bw in rats, dermal LD50 values of > 2910 mg/kg bw in rats and rabbits an inhalation LC50 value (4 h) of >12540 mg/m^3 in rats.

4.3 Irritation

4.3.1 Skin irritation

Previous evaluations

Several studies on skin irritation in rabbits were available but some were of poor quality or incompletely reported the results. One study in 2 male and 4 female rabbits (BASF, 1979c*) reported the presence of mild skin erythema in all animals 24 hours after treatment with 0.5 mL of undiluted DIDP under occlusive dressing. Mild oedema was also observed in 3/6 animals. Skin irritation persisted until day 2 but completely disappeared by day 8. Another study also reported the presence of skin erythema in all of 4 animals 24 hours after treatment with 0.5 mL of undiluted DIDP + 0.5-1% bisphenol A under occlusive dressing. Erythema disappeared after 2 days (BASF, 1979b*).

In a human patch test on 15 subjects with undiluted DIDP applied for 24 hours, no signs of irritation were observed either at 30 minutes or 24 hours (Hill Top Research, 1995*). In another minimally reported human patch test involving 144 patients, 2 patients exhibited an irritation reaction after application of 5% (w/w) DIDP dissolved in petrolatum (Kanerva et al., 1996*). No other details were available.

Data not reported in previous evaluations

Kanerva et al. (1999) reported results from patch testing of patients referred to an occupational dermatology clinic over a 6 year period. Two out of a total of 310 patients tested with 5% DIDP under occlusion for 2 days exhibited irritant reactions.

Conclusion

DIDP causes minimal skin irritation in rabbits and humans.

4.3.2 Eye irritation

Previous evaluations

In a study conducted in 6 rabbits, undiluted DIDP caused slight redness of the conjunctiva in all animals after 1, 4 and 24 hours. No reactions were noted at 48 or 72 hours (Industrial Bio-test Laboratories, 1975*).

In another study conducted in 6 rabbits using a US Food and Drug Administration test methodology, 0.1 mL of undiluted DIDP caused slight redness of the conjunctiva in all animals after 1, 4 and 24 hours. After 72 hours, redness of the conjunctiva was still observed in 3/6 animals (BASF, 1979a*).

In another study conducted in 6 rabbits, 0.1 mL of undiluted DIDP caused slight redness of the conjunctiva in all animals after one hour and 24 hours. No reactions were noted at 48 or 72 hours (Inveresk Research International, 1981*).

In a study conducted in 3 rabbits to OECD test guidelines, 0.1 mL of undiluted DIDP caused redness of the conjunctiva in all animals after one hour. No reactions were noted at 24, 48 or 72 hours (BASF, 1986*).

Corneal opacity was not observed in any study.

Data not reported in previous evaluations

No data.

Conclusion

DIDP causes minimal eye irritation in rabbits.

4.3.3 Respiratory irritation

Previous evaluations

No data.

Data not reported in previous evaluations

No data.

Conclusion

No data were available to determine the respiratory irritant potential of DIDP.

4.4 Sensitisation

Previous evaluations

There were three skin sensitisation studies available in guinea pigs, one Magnusson and Kligman maximisation study (Inveresk Research International, 1981*) and two Buehler studies (Exxon Biomedical Sciences, 1992*; Huntington Research Centre, 1994*). Twenty guinea pigs were treated with DIDP in each study.

Only the 1992 Buehler study reported a clear positive response where upon rechallenge on day 35, eight of 20 animals showed slight erythema with 7 of 20 showing well-defined erythema (score 2). One of 20 control animals showed slight erythema at rechallenge. Although all studies reported the use of either undiluted DIDP or DIDP as Vestinol DZ for induction, none of the studies adequately reported the composition of test substance. In addition, the significance of the negative results in the 1981 and 1994 studies was weakened by a lack of evidence of irritation at the induction phase in these studies.

Two skin sensitisation studies in humans were noted. Medeiros et al. (1999*) described a lack of positive skin reactions in 104 subjects in a patch test applying undiluted DIDP three times per week for three successive weeks. In an irritant and allergic human patch test, 2 of 144 subjects exhibited skin irritant reactions after application of 5% DIDP. None showed allergic reactions (Kanerva et al., 1996*).

A single case of allergic contact dermatitis from DIDP in a PVC identity band was described (Hills and Ive, 1993*). Severe vesicular eczema was observed on both wrists of a 64 year old woman under 2 different examples of the same type of PVC wrist band. Patch tests with the band and 5% DIDP in petrolatum showed positive reactions.

Data not reported in previous evaluations

Kanerva et al. (1999) reported results from patch testing of patients remitted to an occupational dermatology clinic over a 6 year period. None out of a total of 310 patients tested with 5% DIDP under occlusion for 2 days exhibited allergic reactions.

Conclusion

A positive response was reported from one Buehler test. In two negative studies, doses were not sufficient to elicit irritation at induction. Additionally, significant irritation was observed following application of the test substance in the positive study that was not observed in the two negative animal studies. In all three studies, the composition of test substance was not well established. Consequently, a possible confounding effect of impurities or additives could not be disregarded.

In humans, there is only a single case study reporting skin sensitisation from DIDP.

Overall, data indicate that DIDP does not cause skin sensitisation.

4.5 Repeated dose toxicity

Previous evaluations

Oral

Several repeat dose oral toxicity studies were noted by ECB (2003). In short-term studies with DIDP in rats and dogs, the main effects were increased liver weights and lipid metabolism in the liver, in the absence of associated pathology. Repeat dose studies and results are summarised in Table 3. Key studies that include investigations of peroxisome proliferation are described below.

In a 21 day feeding study designed to assess peroxisomal proliferation, Fischer 344 rats (5/sex/dose) were administered DIDP at dietary doses of 0, 0.3, 1.2 and 2.5% (approx 300, 1000 and 2000 mg/kg bw/d) (BIBRA, 1986*). No treatment-related clinical signs were noted. Males at 1.2 and 2.5% and females at 2.5% showed decreases in weight gains during treatment (statistically significant in both sexes at 2.5% dose only). Only males at 2.5% consumed significantly less food throughout the treatment period. Significant increases in absolute and relative liver weights were seen in males at all dose levels and in females at 1.2% and 2.5%. Serum triglycerides and cholesterol levels were reduced only in males at 1.2% and 2.5%. The changes were not dose-related. Cyanide-insensitive palmitoyl-CoA oxidation was significantly increased in all treated animals at 1.2% and 2.5% but not at 0.3%. Significant increases in lauric acid 11- and 12-hydroxylase levels were observed in all treated males, but in females only levels of lauric acid 12-hydroxylase were increased at 2.5%. Electron microscopic examinations revealed marked but variable increases in number and size of hepatocyte peroxisomes in both sexes at 2.5%.

Relative kidney weights were significantly higher in all treated groups except females at 0.3% but absolute kidney weights were lower in both sexes at 2.5% and higher in males at 1.2% and 2.5%. Absolute testis weights of males at 2.5% were slightly but significantly decreased but relative testis weights were significantly increased at this dose. No histological evidence of testicular atrophy was found.

Table 3: Summary of repeat dose studies

Species, study duration, and administration mode	Doses (mg/kg bw/d)	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d) & endpoint	References
Rat 21 days (5/sex/dose), diet	0, 300, 1000, 2000 (approx.)	Male: none Female: 300	300; increased liver weight (absolute and relative) (males)	BIBRA, 1986*
Rat 28 days (5/sex/dose), diet	0, 25, 57, 116, 353, 1287	57	116; increased liver weights, increased cyanide-insensitive palmitoyl-CoA oxidation	Lake et al., 1991*
Rat 3 months (20/sex/dose), diet	Male: 0, 55, 100, 200, 400 Female: 0, 60, 120, 250, 500	Male: 200 Female: 60	Male: 400; increased liver weights (absolute) Female: 120; increased liver weights (relative)	BASF, 1969*
Rat 3 months (10/sex/dose), diet	Male: 0, 28, 170, 586 Female: 0, 35, 211, 686	200	650; increased liver weight	Hazelton Laboratories, 1968a*
Dog 13 weeks (3/sex/dose), diet	0, 15, 75, 300	15	75; increased liver weight, slight to moderate swelling and vacuolation of hepatocytes	Hazelton Laboratories, 1968b*
Rat 2 weeks, 6 h/d, 5 days/week (8 males), inhalation	0, 505 mg/m^3	505 mg/m^3	None; no systemic effects	General Motors Research Laboratories, 1981*

A 28-day dietary study in male Fischer 344 rats (5/dose) of 0, 0.02, 0.05, 0.1, 0.3 and 1% DIDP (approx 0, 25, 57, 116, 353, 1287 mg/kg bw/d) noted no changes in body weight but recorded dose-related increases in absolute (statistically significant at ≥ 0.3%) and relative (statistically significant at ≥ 0.1%) liver weights. Liver palmitoyl-CoA oxidation activity was increased in a statistically significant and dose–related fashion at ≥ 0.1%. No testicular atrophy was reported at the highest dose tested (Lake et al., 1991*).

A 3-month dietary study was conducted in rats (species not specified) (20/sex/dose) using doses of 0, 800, 1600, 3200 and 6400 ppm DIDP (approx. 0, 55-60, 100-120, 200-250 and 400-500 mg/kg bw/d males-females respectively) (BASF, 1969*). No clinical signs of toxicity were noted. No differences in food intake or body weight gains were observed in female rats. In males, food intakes were normal but body weight gains were decreased slightly from day 77 onwards at ≥ 1600 ppm. Absolute liver weights were increased in all males but statistically significantly only at the highest dose (6400 ppm). Relative liver weights were significantly increased in all male animals but without a clear dose-relationship. In females, absolute liver weights were increased significantly at ≥ 3200 ppm (dose-related). Relative liver weights were increased significantly at ≥ 1600ppm. Absolute kidney weights were

unchanged. In males, relative kidney weights were significantly increased in all treated groups but without a dose-relationship. In females, relative kidney weights were increased at 1600 ppm and 3200 ppm but not at the highest dose (6400 ppm). No pathological changes were observed in any organ. In males, a NOAEL of 3200 ppm (200 mg/kg bw/d) was assigned on the basis of increases in absolute liver weights at the highest dose (6400 ppm). In females, a NOAEL of 800 ppm (60 mg/kg bw/d) and a LOAEL of 1600 ppm (120 mg/kg bw/d) were assigned based on increases in relative liver weight.

A 13-week dietary study was conducted in Beagle dogs (3/sex/dose) using doses of 0, 0.05, 0.3 and 1% DIDP (approx 0, 15, 75 and 300 mg/kg bw/d respectively) (Hazelton Laboratories, 1968b*). No clinical signs of toxicity were noted. Three of 6 dogs at the highest dose showed body weight loss. Only in one animal was this related to decreased food consumption. Clinical chemistry analyses were normal. Gross organ examinations at sacrifice did not reveal DIDP-related effects. Liver weights were increased in all animals in a dose-related fashion. Low animal numbers precluded statistical analysis. Microscopic examinations revealed slight to moderate swelling and vacuolation of hepatocytes at 0.3 and 1%. The severity of these changes was not dose-related. Measurements of serum glutamic-pyruvic and glutamic-oxaloacetic transaminases and sulfobromophthalein clearance were unchanged suggesting a lack of overt hepatic damage.

Two 2-generation reproductive toxicity studies also contained information on repeat dose toxicity. In the first study (Exxon Biomedical Sciences, 1997*, Hushka et al., 2001), rats (30/sex/dose) received 0, 0.2, 0.4 or 0.8% of DIDP (approx 0, 103-379, 211-761, 427-1424 mg/kg bw/d, males-females, respectively) in the diet for 10 weeks prior to mating and then during the mating period. Treatment of females continued throughout gestation and lactation. Statistically significant increases in mean absolute liver weights were observed in all females in both P1 and P2 generations, in P1 males at 0.4% and P2 males at 0.8% (Hushka et al., 2001). These were accompanied by dose-dependent microscopic evidence of centrilobular or diffuse hepatocellular hypertrophy. Statistically significant increased absolute kidney weights were observed in all treated male groups and at 0.4% in P1 females and at 0.4 and 0.8% in P2 females. In females, effects on kidney weight were not dose related and microscopically no kidney damage was observed. Microscopic findings in males were reported to be consistent with a male rat-specific alpha-2μ globulin nephropathy. For parental systemic toxicity (both generations), a LOAEL based on liver effects could be established at 0.2% (103-379 mg/kg bw/d). No NOAEL could be derived.

In the second two-generation study (Exxon Biomedical Sciences, 2000*, Hushka et al., 2001), rats (30/sex/dose) received 0, 0.02, 0.06, 0.2 or 0.4% of DIDP (approx 0, 12-40, 33-114, 114-352, 233-747 mg/kg bw/d, males-females, respectively) in the diet for 10 weeks prior to mating and then during the mating period. Treatment of females continued throughout gestation and lactation. Bodyweight gains, mating performance, fertility and pregnancy indices were not affected by treatment. Statistically significant increases in mean absolute liver weights were observed at 0.4% in both sexes of both parental generations and at 0.2% in P2 females. This was consistent with findings from the previous 2-generation study. Also similar to this previous study, statistically significant increases were observed in mean absolute kidney weights in males of both generations at 0.4% and P2 males and females at 0.2%. For parental systemic toxicity, a NOAEL could be derived at 0.06% (33-114

mg/kg bw/d) with a LOAEL of 0.2% (114-352 mg/kg bw/d) based on kidney changes in P2 males and females.

Inhalation

Male rats (8/group) were exposed by inhalation to an aerosol containing 505 mg/m^3 DIDP for 6 hours/day, 5 days/week for 2 weeks (General Motors Research Laboratories, 1981*). No signs of systemic toxicity were observed. Body weight gains were unchanged. On examination at sacrifice, lung tissue showed moderate increases in alveolar septa widths with signs of mixed inflammatory reactions. Histology for liver, spleen and kidney was unremarkable. Haematological and biochemical parameters were not investigated. The NOAEL was 505 mg/m^3 based on only local irritant effects observed at this dose.

Dermal

No data.

Data not reported in previous evaluations

No data.

Conclusion

In rats and dogs, the liver was the primary target organ in oral studies. Several studies reported liver weight and enzyme changes and histological alterations consistent with peroxisome proliferation.

From a 3-month rat dietary study, a NOAEL of 60 mg/kg bw/d and a LOAEL of 120 mg/kg bw/d were identified based on increased relative liver weights in female rats. In this study, the NOAEL for male rats was 200 mg/kg bw/d and the LOAEL was 400 mg/kg bw/d.

In a 13 week diet study in dogs, which is considered a more relevant species to humans with respect to peroxisome proliferation, a LOAEL of 75 mg/kd bw/d with a NOAEL of 15 mg/kg bw/d were reported, based on increased liver weights and histological changes. However, large individual variations within the low numbers of test animals limit the reliability of this study.

4.6 Genetic toxicity

Previous evaluations

Available genotoxicity studies are summarised in Table 4.

Data not reported in previous evaluations

Results of a mouse lymphoma mutation assay were published in 2000 (Barber et al., 2000) and are included in Table 4.

Conclusion

Based on negative results from in vitro bacterial mutation assays, in vitro mouse lymphoma assays and an in vivo mouse micronucleus assay, DIDP is considered non-genotoxic.

Table 4: Summary of genotoxicity studies

Test	Test system (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 bw	N/A	Negative	Hazelton Washington, 1994*

4.7 Carcinogenicity

Previous evaluations

Two in vitro mammalian cell transformation assays were noted. In the first assay, DIDP was tested on Balb/c-3T3 mouse cells (Barber et al., 2000). With an exposure period of 72 hours and incubation over 4 weeks, DIDP did not induce statistically significant increases in transforming activity with concentrations up to 20 µL/mL. In the second assay, Balb/3T3 Clone A31 mouse embryo cells were treated for 20-24 hours and incubated for 4-6 weeks. Transforming frequencies were statistically significantly increased at a dose level of 1 µL/mL but not at 0.01 or 0.1 µL/mL.

No in vivo carcinogenicity studies were available for assessment.

Data not reported in previous evaluations

No data.

Conclusion

No in vivo carcinogenicity studies were available. Positive results were recorded in one of two in vitro transformation assays conducted under different conditions. Overall, data are insufficient to establish the carcinogenic potential of DIDP.

4.8 Reproductive toxicity

Traditional hazard assessments consider effects on fertility separate from developmental toxicity. Fertility is tested by exposing sexually mature adults to a chemical and examining the effects on reproductive capacity. Developmental toxicity is studied by exposing pregnant dams and looking for effects in the foetuses. Chemicals that affect the developing reproductive system following prenatal exposure may also affect sexual maturation or functional reproductive disorders that are only apparent at maturity. Developmental toxicity can therefore lead to effects on fertility and the two endpoints cannot be clearly distinguished.

In this hazard assessment, data are presented on the basis of test procedure. The effects on fertility and development are then discussed separately. Reproductive and developmental toxicity data are summarised in Table 5.

4.8.1 Repeat dose toxicity studies

Previous evaluations

No testicular lesions were reported in repeat dose oral studies in rats at doses up to 2000 mg/kg bw/d (Section 4.5).

4.8.2 Two-generation reproductive toxicity studies

Previous evaluations

Reproductive toxicity was examined in two well-conducted two-generation studies. The results are summarised in Table 5. In the first study (Exxon Biomedical Sciences, 1997*, Hushka et al., 2001), rats (30/sex/dose) received 0, 0.2, 0.4 or 0.8% of DIDP in the diet for 10 weeks prior to mating and then during the mating period. Treatment of females continued throughout gestation and lactation.

Mating performance, fertility and pregnancy indices were not affected by treatment. Statistically significant reductions in bodyweight gains and food intake were observed at 0.8% during the lactation period in females of both generations. Statistically significant increases in mean absolute and relative liver weights were observed at 0.4 and 0.8% in both sexes of both parental generations. These were accompanied by microscopic evidence of hepatocellular hypertrophy. Statistically significant increased absolute and relative kidney weights were observed in all treated-males groups and at 0.4 and 0.8% in females from both parental generations. There were no statistically significant treatment related changes in the reproductive organs of either sex although oestrus cycle was decreased in high dose F0 females. The NOAEL for fertility was 0.8% (427-927 mg/kg bw/d).

The percentage of F1 pups that died at birth and on PND 4 was statistically significantly higher at 0.8% and was outside the historical control range for the laboratory. In the F2 pups, statistically significant reduced survival was observed in all treated groups in a dose-dependent manner during the first four days of lactation that was outside the historical control range. Reduced survival was also observed on lactation day 7 and at weaning at 0.8%.

Postnatal bodyweight gains were reduced in F1 and F2 pups at 0.8%. Mean relative liver weights were significantly increased in F1 male pups at 0.8% and F1 female pups at 0.4% and 0.8%. Hepatic hypertrophy and eosinophilia were observed in F1

and F2 pups at 0.4 and 0.8%. No developmental NOAEL could be identified due to decreased pup survival in the F2 generation at the lowest dose tested (0.2%).

In the second two-generation study (Exxon Biomedical Sciences, 2000*, Hushka et al., 2001), rats (30/sex/dose) received 0, 0.02, 0.06, 0.2 or 0.4% of DIDP in the diet for 10 weeks prior to mating and then during the mating period. Treatment of females continued throughout gestation and lactation.

Bodyweight gains, mating performance, fertility and pregnancy indices were not affected by treatment. Statistically significant increases in mean absolute and relative liver weights were observed at 0.4% in both sexes of both parental generations. Statistically significant increases in mean absolute and relative kidney weights in males of both generations at 0.4% and in F2 males at 0.2% were observed. Relative kidney weights of F1 females at 0.4% and absolute kidney weights in F2 females at 0.2% were also statistically significantly increased. There were no histological lesions or weight changes in the reproductive organs of either sex. The NOAEL for fertility was 0.4% (233-747 mg/kg bw/d).

In F2 pups, mean body weights were statistically significantly reduced in males at 0.4% on postnatal day 14, in 0.4% females on postnatal days 14 and 21 and in 0.2% females on postnatal day 14. The percentage of F2 pups that died on days 1 and 4 of lactation was statistically significantly higher at 0.2 and 0.4% and outside the historical control range. There were no differences in anogenital distance or nipple retention. Age of preputial separation was increased in high dose F2 but not F1 pups. The developmental NOAEL was 0.06% (38 mg/kg bw/d). The LOAEL was 0.2% based on decreased pup survival in the F2 pups.

4.8.3 Developmental toxicity studies

Previous evaluations

In the first study (BASF, 1995; Hellwig et al., 1997), pregnant rats (7-10/dose) were dosed with DIDP by gavage at 0, 40, 200 or 1000 mg/kg bw/d from gestational days (GD) 6 to 15. Maternal toxicity was observed at 1000 mg/kg bw/d and included increased liver weights and vaginal haemorrhage. DIDP did not affect the incidence of malformations although there was some evidence of increased foetal variations. The main variations observed were hydroureter, dilated renal pelves, increased rudimentary cervical ribs (6/10 litters versus 1/10 for controls) and accessory 14^{th} ribs (8/10 versus 1/10 for controls) at 1000 mg/kg bw/d on a per litter basis (statistically significant). The types of skeletal variations at 200 mg/kg bw/d were not reported and not considered treatment-related. The developmental NOAEL in the study was 200 mg/kg bw/d with a LOAEL of 1000 mg/kg bw/d based on increased skeletal variations.

In the second study (Waterman et al., 1999), pregnant rats (25/dose) were administered DIDP by gavage at 0, 100, 500 or 1000 mg/kg bw/d from GD 6 to 15. Maternal toxicity observed at 1000 mg/kg bw/d included reduced bodyweight gains and food consumption. However, these were not significantly different for the whole of gestation (GD 0-21). Similar to the first study, DIDP did not affect the incidence of malformations although there was evidence of increased foetal variations. The main variations observed were dose-related increases in rudimentary lumbar ribs and supernumerary cervical ribs at 500 (statistically significant on a per foetus basis only) and 1000 mg/kg bw/d (statistically significant on a per litter and per foetus basis). In

the absence of more profound signs of developmental toxicity, findings of supernumerary ribs were generally considered minor. The NOAEL for developmental effects in this study on a per litter basis is considered to be 500 mg/kg bw/d.

ECB (2003) and CERHR (2003) differ in the identification of a NOAEL for developmental effects from the Waterman et al. (1999) study. In the EU risk assessment, the NOAEL for development was 500 mg/kg/d based on significant increase in skeletal variations on a per litter basis at the high dose of 1000 mg/kg/d. The CERHR selected a developmental NOAEL of 100 mg/kg bw/d based on the significant incidence of cervical and accessory 14th ribs on a per foetus basis at 500 mg/kg/d. The litter is regarded as the preferred unit for statistical analysis of developmental toxicity studies (ECB, 2003). According to the CERHR, the Waterman et al. data were reanalysed by the study sponsor, using a linearised model approach using generalised estimating equations (GEE) with similar results obtained. In addition, the sponsor also provided benchmark dose results. 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/d for rudimentary lumbar ribs, skeletal variants and supernumerary cervical ribs, respectively.

Data not reported in previous evaluations

No additional data were available.

4.8.4 Mode of action

DIDP was negative for oestrogenic activity in a yeast two-hybrid assay (Nishihara et al., 2000) and in a recombinant yeast assay (Harris et al., 1997). Also, DIDP was not a competitive agonist at the oestrogen receptor in an in vitro competitive ligand-binding assay and did not induce oestrogen receptor-mediated gene expression in MCF-7 cells. In vivo, DIDP did not induce oestrogenic responses in uterotrophic and vaginal cornification assays using immature and mature ovariectomised rats (Zacharewski et al., 1998).

Conclusion

Effects on fertility

No testicular lesions were reported in repeat dose studies (≤ 3 months in duration) in rats at doses up to 2000 mg/kg bw/d. In two-generation reproduction/developmental studies, mating performance, fertility and pregnancy indices were not affected by treatment. There were no histological lesions in the reproductive organs of either sex. The NOAEL for fertility was 0.8% (427-927 mg/kg bw/d) as this was the highest dose used in a two-generation reproductive toxicity study.

Developmental effects

In the multi-generational reproductive/developmental studies in rats, DIDP induced developmental effects. Two multi-generation studies noted decreased pup viability in the F2 generation at 0.2% (134-352 mg/kg bw/d; Exxon Biomedical Sciences, 2000*; Hushka et al., 2001). However, this may be a result of lactational exposure to DIDP.

The developmental study of Waterman et al. (1999) is regarded as the critical study based on the high number of animals per group, precise dosing (gavage) and completeness of data. The critical endpoint was statistically significant increased incidence of foetal variations (rudimentary lumbar ribs and supernumerary cervical ribs). In the absence of more profound signs of developmental toxicity, the supernumerary ribs were generally considered minor. On a per litter basis, the developmental NOAEL was 500 mg/kg bw/d. The other developmental study (Hellwig et al., 1997) noted similar foetal variations with a NOAEL reported of 200 mg/kg bw/d.

Table 5: Summary of reproductive and developmental studies on DIDP in rats

Study type	Doses	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d) & endpoint	Reference
Two-Generation Reproductive/Developmental Studies				
Rat, Crl:CDBR, VAF Plus 30/group Diet	0, 0.2%, 0.4%, 0.8%	Sys: NE Fert : 427-927 (0.8%) Devp: NE	Sys (parental P1+ P2): 103-379 (0.2%): ↑ liver wt, hepatocyte enlargement Fert: NE Devp: 135-379 (0.2%): ↓ F2 pup survival	Exxon Biomedical Sciences, 1997*; Hushka et al., 2001
Rat, Crl:CDBR, VAF Plus 30/group Diet	0, 0.02%, 0.06%, 0.2%, 0.4%	Sys: 33-114 (006%) Fert: 233-524 (0.4%) Devp: 38-114 (0.06%)	Sys (P2 parental): 114-352 (0.2%): ↑ kidney, liver wt in P2 (F1) parents Fert: NE Devp: 134-352 (0.2%): ↓ F2 pup survival and wt.	Exxon Biomedical Sciences, 2000*; Hushka et al., 2001
Developmental Studies				
Rat, Wistar 10/group GD 6 –15 Gavage	0, 40, 200, 1000 mg/kg bw/d	Systemic: 200 Devp: 200	Systemic: 1000: ↑ maternal liver wt & vaginal haemorrhage; Devp: 1000: ↑ skeletal variations (per litter basis)	BASF, 1995; Hellwig et al., 1997
Rat, SD 25/group GD 6 –15 Gavage	0, 100, 500, 1000 mg/kg bw/d	Systemic: 500 Devp: 500	Systemic: 1000: ↓ maternal body wt gain & food consumption; Devp: 1000: ↑ skeletal variations (per litter basis)	Waterman et al., 1999

d
e

devp: development; fert: fertility; NE: not established; sys: systemic; wt: weight

Hazard Characterisation

A full set of toxicity data for DIDP was not available for all health endpoints. For endpoints with missing or incomplete data, information from structurally similar phthalates, where available, was used to extrapolate potential toxicity. Relevant read-across information was obtained from other NICNAS assessment reports for relevant phthalates and the NICNAS Phthalates Hazard Compendium (NICNAS, 200), which contains a comparative analysis of toxicity endpoints across 24 *ortho*-phthalates, including DIDP.

Following single oral gavage doses in rats, absorption of DIDP from the GIT tract was incomplete and decreased as the dose increased. In rats, dermal absorption was observed to be low (2-4%). Absorption of DIDP from the lung following inhalation exposure was approximately 73%. Following absorption, DIDP was rapidly eliminated via urine and faeces. Following oral absorption, the major metabolites detected in urine were phthalic acid and the oxidised monoester derivative, while the parent compound, the oxidised monoester derivative and MIDP were detected in faeces.

DIDP has low acute oral, dermal and inhalation toxicity. It is a mild skin and eye irritant. It is not considered a skin sensitiser. In repeated dose oral studies with DIDP in rats, the main effects at 120 mg/kg bw/d and above were increased liver weights and lipid metabolism in the liver in the absence of associated pathology. The NOAEL was 60 mg/kg bw/d. Liver enlargement was due to hepatocyte hypertrophy. The major biochemical alterations consisted of induction of both peroxisomal (increased acyl-CoA oxidase) and microsomal (lauric acid 11- and 12-hydroxylases) fatty-acid-oxidising activities. The former is considered to be a specific marker of peroxisome proliferation. In a repeated dose toxicity study of limited reliability in dogs, which is considered a more relevant species to humans with respect to peroxisome proliferation, a LOAEL of 75 mg/kd bw/d was reported for increased liver weights and histological changes. The NOAEL was 15 mg/kg bw/d. Current literature indicates that rodents compared to humans are particularly susceptible to peroxisome proliferative effects. In the light of peroxisome proliferative effects observed for DIDP, liver effects from DIDP exposure may not be relevant for humans.

DIDP is considered not to be genotoxic, based on the results collected from in vitro bacterial mutation assays, in vitro mouse lymphoma assays and an in vivo mouse micronucleus assay.

There were no in vivo carcinogenicity studies available for DIDP. One of two in vitro cell transformation assays was positive for transforming potential. The majority of phthalates have not been adequately tested for carcinogenicity (NICNAS, 2008) and so attempts to correlate carcinogenic potential with structural similarities are not possible.

In two 2-generation reproduction studies with rats, DIDP caused increased liver and kidney weights in parental animals and reduced pup survival, which was more pronounced in the F2 pup generation. There was no evidence to indicate that DIDP causes impairment of fertility. No testicular lesions were reported in repeat dose studies in rats at doses up to 2000 mg/kg bw/d. A NOAEL for fertility was determined at 0.8% (427-927 mg/kg bw/d).

In both two-generation studies, pup survival was reduced in the F2 generation. This may be a result of lactational exposure to DIDP. The LOAEL for pup survival was 0.2% (134-352 mg/kg bw/d). The NOAEL was 0.06% (38-114 mg/kg/d).

An increased incidence of foetal variations (rudimentary lumbar ribs and supernumerary cervical ribs) was seen in a rat developmental study. However, in the absence of more profound signs of developmental toxicity, findings of supernumerary ribs were generally considered minor and there were no biologically important findings at ≤ 500 mg. Therefore, a developmental NOAEL of 500 mg/kg bw/d on a per litter basis was determined based on increased skeletal variations at 1000 mg/kg bw/d.

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6. Human Health Hazard Summary Table

Phthalate	Acute Toxicity	Irritation & Sensitisation	Repeated Dose Toxicity	Genetic Toxicity	Carcinogenicity	Fertility	Developmental Toxicity
Diisodecyl phthalate (DIDP)	Oral Rat: LD50 >29100 mg/kg bw Dermal: Rat: LD50 >2910 mg/kg bw Inhalation: Rat: LC50 >12.54 mg/L/4h	Skin Irritation: ME Eye Irritation: ME Skin Sensitisation: negative	Oral Rat: NOAEL = 60 mg/kg bw/d. LOAEL = 120 mg/kg bw/d (f): ↑ liver weight. Dogs: NOAEL = 15 mg/kg bw/d. LOAEL = 75 mg/kg bw/d: ↑ liver weight (low reliability). High doses: ↑ liver and kidney weight; nephropathy (m); PP noted.	In vitro: Negative in bacterial mutation assays and mouse lymphoma assays In vivo: Negative in mouse micronuclei assay	In vitro: Positive in 1 of 2 cell transformation assays. In vivo: No data	Rat: NOAEL = 0.8%; 427-927 (m-f) mg/kg bw/d LOAEL: NE	Two-generation study Rat: NOAEL = 0.06% (38-114 mg/kg bw/d) LOAEL = 0.2% (134-352 mg/kg bw/d): ↓ pup survival in F2 Gestation study Rat: NOAEL = 500 mg/kg bw/d LOAEL = 1000 mg/kg bw/d: ↑ skeletal variations (cervical and lumbar ribs)

ME – minimal effects; NE - not established; PP – peroxisome proliferation; m – male; f – female

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