Human Health Hazard Assessment

Ditridecyl phthalate (DTDP)
(CAS No. 119-06-2)

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INTRODUCTION

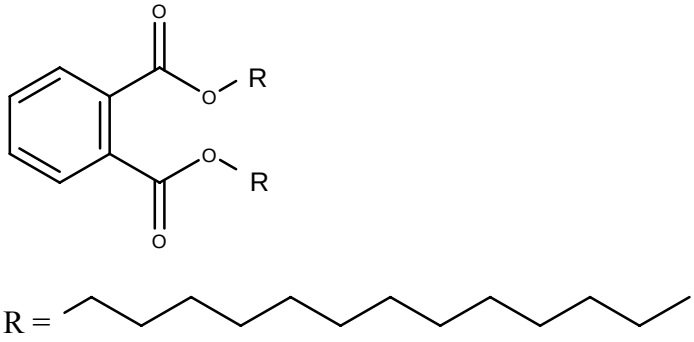
This review of ditridecyl phthalate (DTDP) is a health hazard assessment only. For this assessment, an OECD SIDS Initial Assessment Report on High Molecular Weight Phthalate Esters (HMWPE) (OECD, 2004) was consulted. Information from this report was supplemented with relevant studies from more recent literature surveys conducted up to September 2006.

References not marked with an asterisk were examined for the purposes of this assessment. References not examined but quoted from the key report 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 25 phthalates (NICNAS, 2007).

1. IDENTITY

1.1 Identification of the Substance

CAS Number:	119-06-2
Chemical Name:	1,2-Benzenedicarboxylic acid, ditridecyl ester
Common Name	Ditridecyl phthalate (DTDP)
Molecular Formula:	$C_{34}H_{58}O_4$
Structural Formula:	
	R =
Molecular Weight:	530.8 (based on a di-C13 phthalate ester)
Synonyms:	Ditridecyl phthalate; Bis(tridecyl) phthalate; Phthalic acid, ditridecyl ester.
Purity/Impurities/Additives:	Purity: >99.5% w/w Impurity: 0.1-0.2% w/w anti oxidant Additives: none

1.2 Physicochemical Properties

Table 1: Summary of physicochemical properties

Property	***Value***
Physical state	Colourless liquid
Melting point	-37°C
Boiling point	501°C (101.3 kPa)
Density	950 kg/m^3
Vapour pressure	3.63 x 10^{-11} kPa (25°C)

Water solubility	7×10^{-11} g/L
Partition coefficient n-octanol/water (log Kow)	12.1
Henry's law constant	Not available
Flash point	Not available

Source: OECD (2004)

2. USES

DTDP belongs to a group of phthalates consisting of esters with alkyl carbon backbone of ≥ 7 (High Molecular Weight Phthalate Esters, HMWPEs) (OECD, 2004). According to the European Council for Plasticisers and Intermediates, estimated production of HMWPEs is approximately 60-100 ktonnes per year in Europe. This is likely to represent about one third of world production.

HMWPEs are used primarily as industrial chemicals associated with polymers, mainly as additives to impart flexibility in polyvinyl chloride (PVC) resins, but are also used as synthetic base stocks for lubricating oils. Polymer applications can be divided into PVC-related uses and uses involving other non-PVC polymers. PVC-containing phthalate esters applications can include wire and cable insulation, furniture and automobile upholstery, flooring, wall coverings, coil coatings, pool liners, roofing membranes, and coated fabrics. Polymer-containing phthalate ester applications that are non-PVC based include thermoplastics, rubbers and selected paints and adhesives.

In Australia, DTDP is imported in finished encapsulating and blocking compounds for telephone cable maintenance.

3. HUMAN HEALTH HAZARD

3.1 Toxicokinetics

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

Conclusion

No toxicokinetic studies were available for assessment.

3.2 Acute Toxicity

Previous Evaluations

Study	***Species***	***Results (LD50/LC50)***	***References***
Oral	Rat	>2000 mg/kg bw/d	Japan MHW*

Data not Reported in Previous Evaluations

No data.

Conclusion

DTDP has low acute oral toxicity, with a LD50 for rats of >2000 mg/kg bw/d. No acute toxicity data from inhalation or dermal exposure or human studies were available for DTDP.

3.3 Irritation

Skin Irritation

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

Conclusion

No skin irritation studies were available for assessment.

Eye Irritation

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

Conclusion

No eye irritation studies were available for assessment.

Respiratory Irritation

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

Conclusion

No respiratory irritation studies were available for assessment.

3.4 Sensitisation

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

Conclusion

No sensitisation studies were available for assessment.

3.5 Repeated Dose Toxicity

Previous Evaluations

DTDP was studied for oral toxicity in Sprague-Dawley rats in a combined repeated dose and reproductive/developmental toxicity screening test conducted to OECD test guidelines (Japan MHW, unpublished report*). Doses of 0, 10, 50 and 250 mg/kg bw/day DTDP were administered by gavage in corn oil to males for 42 days and to females from 14 days prior to mating to day 3 of lactation. No deaths were observed. At 50 and 250 mg/kg bw/day, transiently increased salivation was observed in males from day 10 until sacrifice and decreased body weight gain was observed in females at these doses. Increased liver and kidney weights were seen in males at the highest dose (250 mg/kg bw/day) and in females at 50 and 250 mg/kg bw/day.

Histopathological examinations revealed hypertrophy of centrilobular hepatocytes at 50 and 250 mg/kg bw/day in both sexes with increased catalase-positive granules observed in hepatocytes in males. At 250 mg/kg bw/day in males, eosinophilic bodies in renal tubular cells and basophilic tubules in the renal cortex which appeared to be regeneration foci resulting from necrosis of renal tubular epithelium were also observed. Females at this highest dose level had increased hyperplasia of the pelvic epithelium and transitional cells in the bladder. Alkaline phosphatase activity was increased in both sexes at this highest dose.

The NOAEL was considered to be 10 mg/kg/day, with a LOAEL based on increased liver weights, decreased body weight gain and hypertrophy of centrilobular hepatocytes at ≥ 50 mg/kg bw/day.

Data not Reported in Previous Evaluations

No data.

Conclusion

Only one repeat dose study in rats was reported. The liver appeared to be the target organ of DTDP. Hepatoxicity included increased liver weights and hypertrophy of centrilobular hepatocytes. Additionally, DTDP at the highest dose had effects on the kidney, including increased kidney weights, eosinophilic bodies in renal tubular cells and basophilic tubules indicating regeneration foci in the renal cortex. The NOAEL was considered to be 10 mg/kg/day, and the LOAEL being 50 mg/kg bw/d based on liver effects.

3.6 Genetic Toxicity

Previous Evaluations

DTDP was not mutagenic in an Ames tests utilising *S. typhimurium* (TA100, TA1535, TA98, and TA1537) and *E. coli* WP2 uvrA (up to 5000 μg/plate), and did not induce structural chromosomal aberrations or polyploidy in Chinese hamster lung (CHL) cells with or without metabolic activation (up to 4750 μg/plate) (Japan MHW, unpublished report*).

Data not Reported in Previous Evaluations

No data.

Conclusion

DTDP was negative in Ames and *in vitro* chromosome aberration tests. No *in vitro* mammalian mutation and *in vivo* genotoxicity data were available for DTDP.

3.7 Carcinogenicity

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

Conclusion

No carcinogenicity studies were available for assessment.

3.8 Reproductive Toxicity

Previous Evaluations

DTDP was studied for reproductive toxicity in rats in an OECD combined repeat dose and reproductive/developmental toxicity screening test at doses of 0, 10, 50 and 250 mg/kg bw/day (Japan MHW, unpublished report*). The study duration for males was 42 days and for females continued from 14 days prior to mating to day 3 of lactation. Maternal effects included mild suppression of body weight gain (<10% decrease) in females in the 50 mg/kg bw/day group at the end of lactation day 4 and increased liver:body weight ratios in females in the 50 and 250 mg/kg groups. Body weight gain was also decreased in males in the higher dose group. There was no testicular toxicity. There was no effect on number of corpora lutea, implantation sites, number of pups born or born alive or pup weight. However, there was a statistically significant decrease in live birth index possible associated with poor lactation (87.7% in high dose cf 99.6% in controls) and decreased pup viability (not significant; 89.9% in high dose cf 96.8% in controls)) at postnatal day 4 at 250 mg/kg bw/day. However, there were no adverse effects on sex ratio, body weight changes, or morphological appearance of pups. The NOAEL for reproductive and developmental effects was 250 mg/kg bw/d, the highest dose tested.

Data not Reported in Previous Evaluations

No data.

Conclusion

Fertility effects

The combined repeat dose and reproductive/developmental toxicity study on DTDP (a di-C13 PE) showed no significant reproductive toxicity at doses up to 250 mg/kg bw/day.

Developmental Toxicity

The combined repeat dose and reproductive/developmental toxicity study on DTDP (a di-C13 PE) showed no marked developmental effects. Effects included decreased live birth index at 250 mg/kg bw/day, however these effects are considered minor and possibly related to poor lactation.

4. HAZARD CHARACTERISATION

Toxicity data for DTDP were not available for the majority of 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 (2007) which contains a comparative analysis of toxicity endpoints across 25 phthalates, including DTDP.

DTDP is a C13 phthalate and a member of the High Molecular Weight Phthalate Esters (HMWPEs) Category as defined by the Phthalate Esters Panel HPV Testing Group (2001) and OECD (2004). The HMWPE group includes chemically similar substances produced from alcohols having backbone carbon lengths of ≥ C7. Due to their similar chemical structure, category members are generally similar with respect to physicochemical, biological and toxicological properties or display an expected trend. Thus, read-across for toxicity endpoints is an appropriate approach to characterise selected endpoints for members of this category.

Data are not available on the toxicokinetics of DTDP. However, studies on HMWPEs indicate that they are rapidly metabolised in the gastrointestinal tract to the corresponding monoester, absorbed and excreted, primarily in the urine.

DTDP has low acute oral toxicity. No acute dermal or inhalation toxicity studies are available for DTDP. Based on data for other HMWPEs, DTDP is expected to have low acute dermal and inhalation toxicity (NICNAS, 2007). Similarly, DTDP is not likely to cause skin and eye irritation or skin sensitisation.

DTDP was negative in Ames and *in vitro* chromosome aberration tests. No *in vitro* mammalian mutation and *in vivo* genotoxicity data are available for DTDP. However, based on the negative mutagenicity data for the HMWPE Category as a whole, including data on the 7 phthalates reviewed in the NICNAS Phthalate Hazard Compendium (NICNAS, 2007) and other high molecular weight phthalates reviewed by the Phthalate Esters Panel HPV Testing Group (2001) and OECD (2004), there is low likelihood that DTDP is a genotoxic agent.

In the only reported repeat dose study, the liver appeared to be the target organ of DTDP. Increased liver weights and hypertrophy of centrilobular hepatocytes were observed. Additionally, DTDP had effects on the kidney which included increased kidney weights, eosinophilic bodies in renal tubular cells and basophilic tubules in the cortex, but these occurred only at the highest dose. The NOAEL was 10 mg/kg/day, with a LOAEL based on increased liver weights, decreased body weight gain and hypertrophy of centrilobular hepatocytes at ≥ 50 mg/kg bw/day.

No carcinogenicity data are available for DTDP. Due to insufficient testing on phthalates, it is not possible to extrapolate carcinogenic potential for DTDP.

In a combined repeat dose and reproductive/developmental toxicity study in rats (one-generation study), DTDP had no effects on copulation, fertility, delivery, sex ratio, body weight, and morphological appearance of pups. Only poor lactation and slightly decreased

pup viability were observed at the highest dose. There were also no developmental toxicity observed even at the highest dose, although maternal effects including slightly decreased body weight gain, increased relative liver weight and slight liver hypertrophy occurred at the middle and high dose levels. The NOAEL for reproductive and developmental effects was 250 mg/kg bw/d. In addition, none of the high molecular weight phthalates reviewed by NICNAS affected fertility or other aspects of the male reproductive system or induced developmental effects (NICNAS, 2007). Therefore, DTDP is considered unlikely to affect fertility and development.

5. HUMAN HEALTH HAZARD SUMMARY TABLE

Phthalate	***Acute Toxicity***	***Irritation & Sensitisation***	***Repeated Dose Toxicity***	***Genetic Toxicity***	***Carcinogenicity***	***Fertility***	***Developmental Toxicity***
Ditridecyl phthalate (DTDP)	Oral Rat: LD50 >2000 mg/kg bw Dermal No data Inhalation No data	Skin irritation: No data Eye irritation: No data Respiratory irritation: No data Skin sensitisation: No data	Rat: NOAEL = 10 mg/kg bw/d LOAEL = 50 mg/kg bw/d, ↑ liver weights, hypertrophy of centrilobular hepatocytes, ↓ body weight gain. High doses: liver, kidney effects. PP not noted.	*In vitro* Negative in bacterial mutation and chromosomal aberration tests *In vivo* No data	No data	NOAEL = 250 mg/kg bw/day LOAEL = not established	NOAEL = 250 mg/kg bw/day LOAEL = not established

↑: increase; ↓: decrease; PP: peroxisome proliferation

6. REFERENCES

Japan MHW. Toxicity testing reports of environmental chemicals, Ditridecyl phthalate (CAS No. 119-06-2). Japan Ministry of Health & Welfare. Unpublished report.

NICNAS (2007) Phthalate Hazard Compendium: A summary of physicochemical and human health hazard data for 25 phthalate chemicals. Sydney, National Industrial Chemicals Notification and Assessment Scheme.

OECD (2004) SIDS Initial Assessment Report for SIAM 19: Category – High Molecular Weight Phthalate Esters. Organisation for Economic Cooperation and Development, Berlin, Germany, 19-22 October 2004.

Phthalate Esters Panel HPV Testing Group (2001) High production volume (HPV) chemical challenge programme test plan for the phthalate esters category. December 10, 2001.