Existing Chemical Hazard Assessment Report

Australian Government
Department of Health and Ageing
NICNAS

Ditridecyl Phthalate

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME
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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.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with the Department of the Environment, Water, Heritage and the Arts, which carry out the environmental assessment for NICNAS. NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia.

For the purposes of Section 78(1) of the Act, copies of assessment reports for New and Existing Chemical assessments are freely available from the web (www.nicnas.gov.au). Summary Reports are published in the *Commonwealth Chemical Gazette* (http://www.nicnas.gov.au/publications/#gazette), and are available to the public on line at www.nicnas.gov.au.

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Overview

This review of ditridecyl phthalate (DTDP) is a health hazard assessment only. For this assessment, the Organisation for Economic Cooperation and Development, Screening Information Data Set (OECD SIDS) Initial Assessment Report on High Molecular Weight Phthalate Esters (HMWPE) was consulted. Information from this report was 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. DTDP possesses 2 linear ester side chains each with a backbone of 13 carbons (C13). DTDP is considered to belong to the HMWPE group of phthalates consisting of esters with alkyl carbon backbone of $\geq$ C7. According to the European Council for Plasticisers and Intermediates, estimated production of HMWPE is approximately 60-100 ktonnes per year in Europe. This is likely to represent about one third of world production.

HMWPE 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.

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 hazard assessment reports for phthalates and the NICNAS Phthalates Hazard Compendium, which contains a comparative analysis of toxicity endpoints across 24 *ortho*-phthalates, including DTDP.

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

DTDP has low acute oral toxicity. No acute dermal or inhalation toxicity studies were available for DTDP. Based on data for other HMWPE, DTDP is expected to have low acute dermal and inhalation toxicity. 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 were available for DTDP. However, based on the negative mutagenicity data for the HMWPE Category as a whole, including data on the seven phthalates reviewed in the NICNAS Phthalate Hazard Compendium and other HMWPE reviewed by the Phthalate Esters Panel HPV Testing Group and OECD, DTDP is unlikely to be genotoxic.

In the only reported repeat dose study, the liver appeared to be the target organ of DTDP. Additionally, DTDP had effects on the kidney but these occurred only at the highest dose. The NOAEL was 10 mg/kg/d, with a LOAEL based on increased liver weights, decreased body weight gain and hypertrophy of centrilobular hepatocytes at 50 mg/kg bw/d.

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

In a combined repeat dose and reproductive/developmental toxicity study in rats (one-generation study), poor lactation and slightly decreased pup viability were observed at the highest dose. There were no reproductive effects and developmental toxicity observed even at the highest dose, although maternal effects occurred at the middle and high dose levels. The NOAEL for reproductive and developmental effects was 250 mg/kg bw/d, the highest dose tested.

Overall, none of the other studies of HMWPE (except isononyl phthalate, DINP) reviewed by NICNAS revealed effects on fertility or other aspects of the male reproductive system. DTDP therefore may be similarly considered not to show significant effects on fertility. The HMWPE appear generally to induce slight developmental effects at high doses. Increased frequencies of skeletal variations, common variations seen in developmental studies, were observed following gestational exposure to some HMWPE at high doses. Therefore, exposure to DTDP may have similar slight adverse developmental effects at high doses.

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Acronyms and Abbreviations

bw	body weight
C	Celsius
CAS	Chemical Abstracts Service
d	day
DTDP	ditridecyl phthalate
g	gram
HMWPE	High Molecular Weight Phthalate Esters
HPV	High production volume
kg	kilogram
kPa	kilopascals
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LOAEL	lowest-observed-adverse-effect level
mg	milligram
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Cooperation and Development
PVC	polyvinyl chloride
SIDS	Screening Information Data Set
w/w	weight per weight
µ	Micro

1. Introduction

This review of ditridecyl phthalate (DTDP) is a health hazard assessment only. For this assessment, the Organisation for Economic Cooperation and Development, Screening Information Data Set (OECD SIDS) Initial Assessment Report on High Molecular Weight Phthalate Esters (HMWPE) (OECD, 2004) was consulted. Information from this report was supplemented with literature surveys conducted up to September 2006.

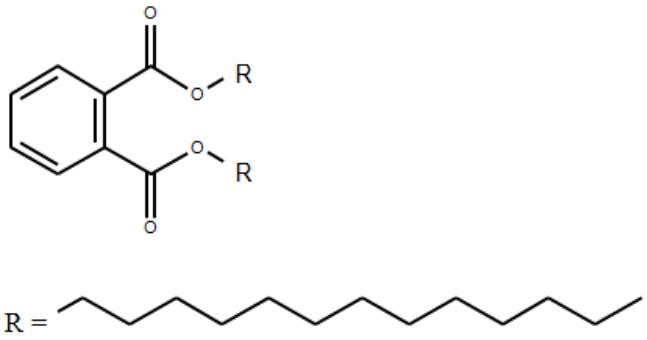
Information on Australian uses was compiled from data supplied by industry in 2004 and 2006.

References not marked with an asterisk were examined for the purposes of this assessment. References not examined but quoted from 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 24 phthalates (NICNAS, 2008).

2. Identity

2.1 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:	
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

2.2 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	3.63×10^{-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)

3. Uses

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

HMWPE 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.

4. Human Health Hazard

4.1 Toxicokinetics

Previous evaluations

No data.

Data not reported in previous evaluations

No data.

Conclusion

No toxicokinetic studies were available for assessment.

4.2 Acute toxicity

Previous evaluations

Study	Species	Results (LD50/LC50)	References
Oral	Rat	>2000 mg/kg bw	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.

4.3 Irritation

4.3.1 Skin irritation

Previous evaluations

No data.

Data not reported in previous evaluations

No data.

Conclusion

No skin irritation studies were available for assessment.

4.3.2 Eye irritation

Previous evaluations

No data.

Data not reported in previous evaluations

No data.

Conclusion

No eye irritation studies were available for assessment.

4.3.3 Respiratory irritation

Previous evaluations

No data.

Data not reported in previous evaluations

No data.

Conclusion

No respiratory irritation studies were available for assessment.

4.4 Sensitisation

Previous evaluations

No data.

Data not reported in previous evaluations

No data.

Conclusion

No sensitisation studies were available for assessment.

4.5 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/d 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/d, 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/d) and in females at 50 and 250 mg/kg bw/d.

Histopathological examinations revealed hypertrophy of centrilobular hepatocytes at 50 and 250 mg/kg bw/d in both sexes with increased catalase-positive granules observed in hepatocytes in males. At 250 mg/kg bw/d 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/d, with a LOAEL based on increased liver weights, decreased body weight gain and hypertrophy of centrilobular hepatocytes at ≥ 50 mg/kg bw/d.

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 bw/d, and the LOAEL being 50 mg/kg bw/d based on liver effects.

4.6 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.

4.7 Carcinogenicity

Previous evaluations

No data.

Data not reported in previous evaluations

No data.

Conclusion

No carcinogenicity studies were available for assessment.

4.8 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/d (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/d 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/d. 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/d.

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/d, however these effects are considered minor and possibly related to poor lactation.

5. 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 (NICNAS, 2008) which contains a comparative analysis of toxicity endpoints across 24 *ortho*-phthalates, including DTDP.

DTDP is a C13 phthalate and a member of the High Molecular Weight Phthalate Esters (HMWPE) Category as defined by the American Chemistry Council 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 HMWPE indicate that they are rapidly absorbed and metabolised to the corresponding monoester in the gastrointestinal tract, 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 HMWPE, DTDP is expected to have low acute dermal and inhalation toxicity (NICNAS, 2008). 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 seven phthalates reviewed in the NICNAS Phthalate Hazard Compendium (NICNAS, 2008) 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/d, with a LOAEL based on increased liver weights, decreased body weight gain and hypertrophy of centrilobular hepatocytes at ≥ 50 mg/kg bw/d.

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, the highest dose tested.

Overall, none of the other studies of high molecular weight phthalates (except isononyl phthalate, DINP) reviewed by NICNAS revealed effects on fertility or other aspects of the male reproductive system. DTDP therefore may be similarly considered not to show effects on fertility. The high molecular weight phthalates appear generally to induce slight developmental effects at high doses (NICNAS, 2008). Increased frequencies of skeletal variations, common variations seen in developmental studies, were observed following gestational exposure to some high molecular weight phthalates at high doses. Therefore, exposure to DTDP may have similar slight adverse developmental effects at high doses.

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6. 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/d LOAEL = not established	NOAEL = 250 mg/kg bw/d LOAEL = not established

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

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References

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

NICNAS (2008) Phthalate hazard compendium: a summary of physicochemical and human health hazard data for 24 *ortho*-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. Prepared by:ExxonMobil Biomedical Sciences, Inc. for the Phthalate Esters Panel HPV Testing Group of the American Chemistry Council. http://www.epa.gov/hpv/pubs/summaries/benzene/c13467tc.htm (Accessed 2007).