Human Health Hazard Assessment

Diundecyl phthalate (DUP)
(CAS No. 3648-20-2)

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INTRODUCTION

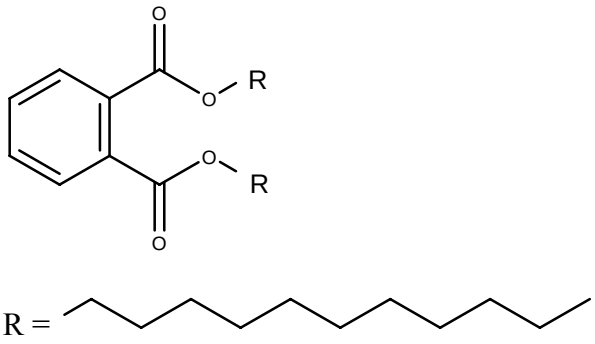
This review of diundecyl phthalate (DUP) is a health hazard assessment only. For this assessment, an OECD SIDS Initial Assessment Report on High Molecular Weight Phthalate Esters (HMWPE) (OECD, 2004) was consulted. Information from this report was supplemented with relevant studies from more recent literature 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:	3648-20-2
Chemical Name:	1,2-Benzenedicarboxylic acid, diundecyl ester
Common Name:	Diundecyl phthalate (DUP)
Molecular Formula:	$C_{30}H_{50}O_4$
Structural Formula:	
	R =
Molecular Weight:	474.7 (based on a di-C11 phthalate ester)
Synonyms:	Phthalic acid, diundecyl ester; Undecyl alcohol, phthalate
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	-9°C
Boiling point	501°C (101.3 kPa)
Density	954 kg/m^3
Vapour pressure	4.97 x 10^{-10} kPa (25°C)

Water solubility	4.41×10^{-9} g/L
Partition coefficient n-octanol/water (log Kow)	10.3 (25°C)
Henry's law constant	Not available
Flash point	Not available

Source: OECD (2004)

2. USES

DUP belongs to a group of phthalates consisting of esters with alkyl carbon backbone of 7 carbon atoms or greater (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, DUP is imported for use in photographic paper dispersion coating, printing inks and flame-retardant polyurethane resins for construction.

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

In an acute oral study in rats a LD50 >15800 mg/kg bw was reported for a di-C11 PE (whether DUP, CAS No. 3648-20-2 or DIUP, CAS No. 85507-79-5 was not specified) (Krauskopf, 1973*).

In an intraperitoneal (ip) toxicity study in mice a di-C11 PE (whether DUP or DIUP was not specified) at a dose of 2400 mg/kg bw did not cause any deaths (Nematollahi et al., 1967*).

In an inhalation study, LC50 >1.80 mg/L (vapour) was reported for 6-hour DUP exposure in rats (Monsanto, 1982*).

Data not Reported in Previous Evaluations

No data.

Conclusion

The acute oral toxicity for a di-C11 phthalate ester is low, with LD50 >15800 mg/kg bw. However, the CAS No. was not available to determine whether the data was for DUP (CAS No. 3648-20-2) or DIUP (CAS No. 85507-79-5). When tested at 1.80 mg/L (vapour) in rats, DUP produced no deaths or signs of toxicity. No acute toxicity data from dermal exposure or human studies were available for DUP.

3.3 Irritation

Skin Irritation

Previous Evaluations

DUP was non-irritating in rabbits with a Primary Irritation Index of 0 on a scale of 0-8 (Monsanto, 1982*).

In preparation for skin sensitisation testing in a Human Repeated Insult Patch Test (HRIPT), 15 subjects were exposed to a group of C6 to C13 phthalates, including DUP. Undiluted test substances were individually applied to the skin under an occluded patch for 24 hours and readings were taken at 30 min and 24 h after patch removal. No significant irritation was noted from any of the substances, which included DUP (Medeiros et al., 1999).

Data not Reported in Previous Evaluations

No data.

Conclusion

DUP did not cause skin irritation in rabbit or human patch tests.

Eye Irritation

Previous Evaluations

DUP was found to cause minimal irritation to the eyes of rabbits with a Draize score of 4 on a scale of 0 to 110 (Monsanto, 1982*).

Data not Reported in Previous Evaluations

No data.

Conclusion

DUP caused minimal eye irritation in rabbits.

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

A Human Repeated Insult Patch Test (HRIPT) was conducted in 104 people exposed to a group of C6 to C13 phthalates using the modified Draize procedure. Undiluted test substances (which included DUP) were individually applied to the skin 3 times per week for 3 successive weeks during the induction and challenge phases. No evidence of skin sensitisation was noted from exposure to DUP or to any of the phthalates (Medeiros et al., 1999).

Data not Reported in Previous Evaluations

No data.

Conclusion

DUP did not induce dermal sensitisation in human patch tests.

3.5 Repeated Dose Toxicity

Previous Evaluations

DUP was tested in Fischer 344 rats (5/sex/dose) for 21 continuous days at 0, 0.3, 1.2, or 2.5% in the feed (approximately 0, 282, 1145 or 2305 mg/kg bw/d) (BIBRA, 1985*; Barber et al., 1987*). Statistically significant decreases in body weight gain were observed in mid- and high-dose animals. At the mid- and high-dose, liver and kidney weights were increased and the liver weight effects were dose-related. In addition, increases were seen in liver enzymes and palmitoyl-CoA (PCoA) oxidation which are indicators of peroxisome proliferation. Mid and high dose males showed dose-related increases in relative testes weight. However, absolute weights remained unchanged compared to controls and the increases in relative weights were similar to historical controls. A NOAEL of 0.3% (approximately 282 mg/kg

bw/day) and a LOAEL of 1145 mg/kg bw/d were established for the study, based on dose-related changes in liver weights.

Data not Reported in Previous Evaluations

No data.

Conclusion

The liver and kidneys are the primary organs affected by repeated oral doses of DUP. Effects on the liver include increased liver weights and elevated levels of liver enzymes and PCoA oxidation, indicative of peroxisome proliferation. A NOAEL was established at 282 mg/kg bw/d and a LOAEL at 1145 mg/kg bw/d in a 21 day repeated dose study in rats, based on dose-related changes in liver weights.

3.6 Genetic Toxicity

Previous Evaluations

DUP was non-mutagenic in the Ames test using *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 at concentrations up to 10 mg/plate (in 0.1 M sodium phosphate buffer), in the presence and absence of S-9 metabolic activation (Zeiger et al., 1985*). A point to note is that strains that will detect point mutations at A-T sites mutations, such as *S. typhimurium* TA102 or E-coli WP2 uvrA, and cross-linkage agents, such as *S. typhimurium* TA102 or WP2 pKM101, were not tested.

DUP has also shown no mutagenic activity in an *in vitro* mouse lymphoma assay with or without metabolic activation at concentrations up to 10 µl/ml (Barber et al., 2000*).

Data not Reported in Previous Evaluations

No data.

Conclusion

DUP was negative in bacterial and mammalian mutation assays. No *in vitro* cytogenetic and *in vivo* genotoxicity data were available for DUP.

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

In a repeated dose toxicity study described in Section 3.5, DUP was tested in Fischer 344 rats (5/sex/dose) for 21 continuous days at 0, 0.3, 1.2, or 2.5% in the feed (approximately 0, 282, 1145 or 2305 mg/kg bw/day) (BIBRA, 1985*; Barber et al., 1987*). Mid and high dose males showed dose-related increases in relative, but not absolute, testes weight however the relative weights were within historical control range.

DUP was negative for estrogenic activity in recombinant yeast assay (Harris et al., 1997*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Fertility effects

In a 21-day repeated dose toxicity study in rats, DUP doses at and above 1145 mg/kg bw/day were associated with increased relative testes weight albeit within historical control range.

Developmental Toxicity

No data.

4. HAZARD CHARACTERISATION

Toxicity data for DUP 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 DUP.

DUP is a C11 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 health assessment is an appropriate approach to characterise selected endpoints for members of this category.

Data are not available on the toxicokinetics of DUP. 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.

DUP is expected to exhibit low acute oral and dermal toxicity based on data obtained on other high molecular weight phthalates. When tested at 1.8 mg/L (vapour) in rats, DUP produced no deaths or signs of toxicity. DUP caused minimal eye irritation in rabbits and did not cause skin irritation or sensitisation in humans.

DUP is negative in bacterial and mammalian mutation assays. In addition, 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 Phthalate Esters Panel HPV Testing Group (2001) and OECD (2004), there is a low likelihood that DUP is genotoxic.

In a 21-day repeat dose feeding study in rats, DUP induced statistically significant decreases in body weight gain and increases in liver and kidney weights. The liver weight increases were dose-related. In addition, liver enzymes and palmitoyl-CoA (PCoA) oxidation were also increased, further indicators of peroxisome proliferation. A NOAEL of 0.3% (approximately 282 mg/kg bw/day) and a LOAEL of 1145 mg/kg bw/d were established for the study, based on dose-related changes in liver weights

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

Reproductive toxicity data are limited to a 21-day repeated dose toxicity study in rats where DUP was associated with increased relative testes weight, yet these were within the historical control range at 1145 and 2305 mg/kg bw/day. There are no fertility or developmental toxicity studies for DUP. However, 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, DUP is considered unlikely to affect fertility or development.

5. HUMAN HEALTH HAZARD SUMMARY TABLE

Phthalate	***Acute Toxicity***	***Irritation & Sensitisation***	***Repeated Dose Toxicity***	***Genetic Toxicity***	***Carcinogenicity***	***Fertility***	***Developmental Toxicity***
Diundecyl phthalate (DUP)	Oral Rat: LD50 >15800 mg/kg bw Dermal No data Inhalation Rat: LC50 >1.8 mg/L/6h	Skin irritation: Negative Eye irritation: Minimal effects Respiratory irritation: No data Skin sensitisation: Negative	Oral Rat: NOAEL = 282 mg/kg bw/d LOAEL: 1145 mg/kg bw/d, dose related ↑ liver weights. High doses: ↑ liver and kidney weights. PP noted.	*In vitro* Negative in bacterial mutation and mouse lymphoma assays *In vivo* No data	No data	No data	No data

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

6. REFERENCES

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