

Human Health Hazard Assessment

**Di-C7-9 alkyl phthalate (Di-C7-9 PE)
(CAS No. 68515-41-3)**

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INTRODUCTION

This review of Di-C7-9 alkyl phthalate (Di-C7-9 PE) 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.

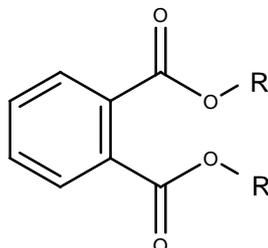
References not marked with an asterisk were examined for the purposes of this assessment. References not examined but quoted from the key report as secondary citations are also noted in this assessment and marked with an asterisk.

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 Numbers:	68515-41-3
Chemical Name:	1,2-Benzenedicarboxylic acid, di-C7-9-branched and linear alkyl esters
Common Name	Di-C7-9 alkyl phthalate (Di-C7-9 PE)
Molecular Formula:	C ₂₄ H ₃₈ O ₄
Structural Formula:	



Molecular Weight:	R = C ₇ H ₁₅ to C ₉ H ₁₉ (branched and linear) [>80% linear] 390.6 (based on a di-C8 phthalate ester)
Synonyms:	Di-C7-9 branched and linear alkyl ester; Dialkyl C7-C9 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

<i>Property</i>	<i>Value</i>
Physical state	Colourless liquid
Melting point	-48°C to -45°C
Boiling point	398°C to 454°C (101.3 kPa)
Density	965 kg/m ³

Vapour pressure	(6.81 – 93.30) x 10 ⁻⁹ kPa (25°C)
Water solubility	(6.10 – 170) x 10 ⁻⁷ g/L
Partition coefficient n-octanol/water (log Kow)	6.9 – 8.6
Henry's law constant	Not available
Flash point	Not available

Source: OECD (2004)

2. USES

Di-C7-9 PE 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, Di-C7-9 PE is imported as a plasticiser for automotive refinishing paints.

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

<i>Study</i>	<i>Species</i>	<i>Results (LD50/LC50)</i>	<i>References</i>
Oral	Rat, Mouse, Guinea pig	>15000 mg/kg bw	Statsek, 1980*
	Rat, Mouse	>19300 mg/kg bw	Brown et al., 1970*
	Rat, Mouse	>20000 mg/kg bw	Gaunt et al., 1968*
Intraperitoneal	Rat, Mouse	>20000 mg/kg bw	Gaunt et al., 1968*

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C7-9 PE has low acute oral and intraperitoneal toxicity in laboratory animals. No acute toxicity data from inhalation or dermal exposure or human studies were available for Di-C7-9 PE.

3.3 IrritationSkin Irritation*Previous Evaluations*

Di-C7-9 PE was not irritating in rabbits when applied as 1 ml of undiluted substance under occluded conditions (Brown et al., 1970*); not irritating in rats or mice when applied at 2000, 4000 or 6000 mg/kg bw (Statsek, 1980*); and not irritating in guinea pigs (Timofievskaya et al., 1988*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C7-9 PE did not cause skin irritation in laboratory animals.

Eye Irritation*Previous Evaluations*

Di-C7-9 was not irritating in rabbit eyes (Brown et al., 1970*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C7-9 PE did not cause 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

In a Maximization test, no skin sensitisation was observed in guinea pigs treated with Di-C7-9 PE (Brown et al., 1970*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C7-9 PE did not induce skin sensitisation in guinea pigs.

3.5 Repeated Dose Toxicity

Previous Evaluations

Oral

Di-C7-9 PE was given to Carworth Farm E rats (15/sex/dose) for 90 days at dose levels of 0, 0.125, 0.25, 0.5 and 1.0% in the feed (approximately 60, 120, 240 and 480 mg/kg bw/d) and gross and microscopic histopathology, urinalysis, haematology and serum chemistry analyses were performed (Gaunt et al., 1968*). At 0.25% and above, there were indications of dose related decreased haemoglobin levels and red blood cell counts, as well as increased urinary cell excretion. At 0.5% and above, haematocrit, haemoglobin and red blood cell counts were clearly reduced, while relative liver and kidney weights were increased. The findings suggested a slight anaemia at dietary levels of 0.25% or more. At 1.0%, males grew more slowly and were unable to concentrate urine normally, with two males producing renal casts. Relative weights of the brain and gonads were increased in males, and both sexes had increased haemosiderin in the spleen. No effects were noted at the lowest dose (0.125%; approximately 60 mg/kg bw/d), and the LOAEL was 0.25% (120 mg/kg bw/d) based on haematological effects.

The repeat dose toxicity of Di-C7-9 PE was assessed as part of a multi-generation reproductive study in Sprague-Dawley rats. Parent animals (28 rats/sex) were given test compounds in diet at dose of 0, 0.1, 0.5, or 1.0% (approx. 0, 100, 500, 1000 mg/kg bw/d) for 10 weeks prior to mating. The 1.0% males showed reduced body weights in both the F0 and F1 generations. The results showed the liver to be the target organ. Liver changes indicative of peroxisome proliferation were noted in both generations and both sexes at the high dose (1%), characterized by increased liver weight in young rats, histopathological changes in mature rats, and an increase in palmitoyl CoA oxidase activity. A NOAEL of 0.5% (500 mg/kg bw/d) and a LOAEL of 1000 mg/kg bw/d were established for systemic toxicity, based

on the toxic effects to the liver (weight and histology) (Willoughby et al., 2000). The reproductive effects are discussed in Section 3.8.

Dermal

Three-week dermal toxicity/irritation studies have been conducted using mixtures containing Di-C7-9 and Di-C9-11 PEs (Brown et al., 1970*). Testing was conducted using rabbits and guinea pigs. One mL undiluted substance was applied to non-occluded, shaved skin of rabbits for 5 days/week for 3 weeks. The skin was assessed daily for gross damage and was examined histopathologically at the end of the studies. No signs of toxicity were seen. Guinea pigs were treated similarly, but the daily dose was 0.5 ml of neat substance. Application of the mixtures to the guinea pigs produced coarse, slightly thickened skin with some apparent sloughing of the surface layers. No overt signs of toxicity were reported for either rabbits or guinea pigs. No other details of the studies were available.

In a study of hepatic and testicular effects, Di-C7-9 PE at a dose of 2500 mg/kg bw/d was administered via gavage to Wistar rats of both sexes for 7 or 21 days (Mangham et al., 1981). Treatment induced statistically significant increases in relative liver weight in both sexes at both timepoints and statistically significant decreases in relative testes weight in males at 21 days only. Male rats showed moderate swelling of centrilobular and midzone hepatocytes at 7 days and of hepatocytes in all lobule zones at 21 days. Fatty vacuolation was also observed in some livers. These changes were less marked in females. Centrilobular degeneration was accompanied by acute inflammation in both sexes.

Data not Reported in Previous Evaluations

In male rats, electron microscopy revealed liver changes as early as day 7 consisting of condensed cell nuclei with crenated nuclear membranes and vacuolated endoplasmic reticulum, the cisternae of which was distended with flocculent granular material. Mitochondria showed signs of degeneration with increased numbers of dense bodies and condensation of the matrix. In female rats, changes were limited to slight proliferation of smooth endoplasmic reticulum and increases in numbers of lysosomes. Lipid droplets were present as large intracytoplasmic bodies. No increases in numbers of peroxisomes were noted in either sex.

Mitochondrial succinate dehydrogenase was depressed in male but not female rats, in accord with the degenerative mitochondrial changes seen in males. Certain enzymatic markers of xenobiotic metabolism were elevated in female rats, but a marked inhibition of xenobiotic metabolism was noted in males.

In testes, Di-C7-9 PE induced bilateral tubular atrophy, with 50-100% of tubules affected in all males after 21 days.

Conclusion

Several repeat dose oral toxicity studies in different rat species indicate that the liver and to a lesser extent the kidney and testes were the main target organs for Di-C7-9 PE. A 90-day oral study in rats noted alterations in haematological and renal parameters and increases in liver and kidney weights. The repeat dose oral NOAEL in rats was 60 mg/kg bw/day, and the LOAEL was 120 mg/kg bw/day, based on decreased haemoglobin levels and red blood cell counts, as well as increased urinary cell excretion.

A multi-generational dietary study in Sprague-Dawley rats, using larger doses, reported peroxisome proliferation in both generations and both sexes, increased liver weight in young rats, histopathological changes and decreased body weights in mature rats and an increase in palmitoyl-CoA oxidase activity at 1000 mg/kg bw/d. A high dose (2500 mg/kg bw/d) 7 and 21-day study in Wistar rats noted both overt and ultrastructural evidence of hepatic toxicity, especially in males. Testicular effects were also observed.

In a limited study, Di-C7-9 PE mixtures did not exhibit any repeated dose toxicity when applied dermally to rabbits and guinea pigs for 3 weeks.

3.6 Genetic Toxicity

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

Conclusion

No genotoxic studies were available for assessment.

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

Traditional hazard assessments consider reproductive toxicity separate from developmental toxicity. Reproductive toxicity is tested by exposing sexually mature adults to a chemical and examining the effects on the animal capacity to reproduce. Developmental toxicity is studied by exposing pregnant dams and looking for effects in the foetuses. However, these tests generally do not detect chemicals that induce effects that only appear postnatally. Thus, 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 reproductive toxicity and the two endpoints cannot be clearly distinguished.

In this hazard assessment, data will be presented on the basis of test procedure, including two-generation studies, developmental/prenatal toxicity studies (only the dam is dosed, study ends before parturition) and developmental/postnatal studies (dam is dosed during gestation and allowed to litter, study ends during weaning). The effects on fertility and development will then be discussed separately in the conclusion.

3.8.1 Two-generation reproductive toxicity studies

Previous Evaluations

Di-C7-9 PE was tested in a two-generation reproductive toxicity study using Sprague-Dawley rats. The test substance was administered daily over 2 generations to 28 animals/sex from 10 weeks prior to mating in F0 generation at dietary levels of 0, 0.1, 0.5, and 1.0% (0, 100, 500, 1000 mg/kg bw/day) (Willoughby et al., 2000). Systemic toxicity was observed at 1000 mg/kg bw/day (liver changes, decreased body weight). The 1.0% (1000 mg/kg bw/day) males showed reduced body weights in both the F0 and F1 generations. There was no impairment of fertility, fecundity, or development in either generation, but pup body weights were slightly reduced in the 1.0% group over the weaning period. There was no effect on preputial separation or time of vaginal opening in the F1 offspring. Ovarian weights were decreased in the 1.0% group for both generations, although ovarian function as assessed by oestrus cycle and mating behaviour was not affected. Absolute and relative testes weight were increased in F1 in high dose group and relative testes weight in F0 high dose group. Relative epididymal weights were increased and absolute seminal vesicle weights were decreased in high dose males of both generations. Under the conditions of the study, Di-C7-9 PE did not impair reproductive function in rats at dietary levels that induce systemic toxicity. The NOAEL for effects on fertility and development was established at 1%, the highest dose used (1000 mg/kg bw/day).

3.8.2 Developmental toxicity studies

Previous Evaluations

In an OECD standard developmental toxicity study, Di-C7-9 PE was administered daily by oral gavage to mated female Sprague-Dawley rats (22/group) at doses of 0 (olive oil), 250, 500, and 1000 mg/kg bw/day from gestation day (GD) 1 through GD 19. On GD20, the animals were sacrificed and the foetuses were examined (Fulcher et al., 2001). There were no signs of maternal toxicity. There were no statistically significant differences in body weight, fertility, reproductive organs, litter size, placental weights or foetal survival between any treatment and control groups at any time during gestation. There were no effects on the incidence of external or visceral abnormalities. An increased incidence of dilated renal pelvis in pups was observed at 250 mg/kg bw/day without a significant dose-related trend. Pups of the high dose group also showed significantly increased incidences of rudimentary supernumerary lumbar ribs (46.4% at high dose compared with 11.8% in controls) in a dose-responsive trend. The frequency of supernumerary ribs was outside historical controls for the laboratory but within historical range for the strain of rat. Under the conditions of this study, Di-C7-9 PE did not induce maternal toxicity, embryo-foetal lethality or teratogenicity. The NOAEL for maternal toxicity was 1000 mg/kg bw/day and for developmental toxicity was 500 mg/kg bw/day. The LOAEL for developmental toxicity was 1000 mg/kg bw/day based on minor skeletal variations.

Data not Reported in Previous Evaluations

No data.

Conclusion

Effects on fertility

The two-generation reproductive toxicity study on Di-C7-9 PE showed no significant reproductive toxicity at doses up to 1000 mg/kg bw/day. Minor effects included slightly decreased ovary weight, transiently decreased body weights, and a decreased pup weight during weaning. The NOAEL for fertility is 1000 mg/kg bw/day.

Developmental effects

Data from the developmental toxicity test on Di-C7-9 PE showed no maternal toxicity, at doses up to 1000 mg/kg bw/day. Although no teratogenic effects were seen, increased frequency of supernumerary lumbar ribs was observed. The NOAEL for development toxicity was 500 mg/kg bw/day, and the LOAEL was 1000 mg/kg bw/day, based on minor skeletal variations.

4. HAZARD CHARACTERISATION

Toxicity data for Di-C7-9 PE were 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 (2007) which contains a comparative analysis of toxicity endpoints across 25 phthalates, including Di-C7-9 PE.

Di-C7-9 PE is 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 ≥ 7 . 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 Di-C7-9 PE. 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.

Di-C7-9 PE has low acute oral and intraperitoneal toxicity. No dermal or inhalation toxicity studies are available for Di-C7-9 PE. Based on data for other HMWPEs, Di-C7-9 PE is expected to have low acute dermal and inhalation toxicity (NICNAS, 2007). Di-C7-9 PE did not cause skin or eye irritation or skin sensitisation in animals.

Di-C7-9 PE has not been tested for genotoxicity. However, Di-C7-9 PE is considered unlikely to be genotoxic 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). The outcome of this read-across approach to characterise the genotoxicity potential for high molecular weight phthalates is in accordance with the general understanding that chemicals with bulky substituents and high molecular weight are likely to be of lower genotoxic potential than their smaller counterparts because they are less effective in interacting with DNA.

Repeat dose oral studies on Di-C7-9 PE revealed the liver, kidney and testes as target organs in different rat species. In Carworth Farm E rats, decreased haemoglobin levels and red blood cell counts, as well as increased urinary cell excretion at higher doses were observed. At higher doses in studies with Sprague-Dawley and Wistar rats, effects included increased cyanide-insensitive palmitoyl-CoA (PCoA) levels, increased liver weights and liver hypertrophy (indicative of peroxisome proliferation). In the latter species with the highest dose, overt and ultrastructural evidence of hepatic toxicity was seen. Testicular effects were also noted. The repeat dose oral NOAEL from a 90-day study was 60 mg/kg bw/day, and the LOAEL was 120 mg/kg bw/day, based on decreased haemoglobin levels and red blood cell counts, as well as increased urinary cell excretion.

No carcinogenicity data are available for Di-C7-9 PE. Due to insufficient testing on other phthalates, it is not possible to extrapolate carcinogenic potential for Di-C7-9 PE.

The multi-generation reproductive toxicity study on Di-C7-9 PE showed no significant reproductive toxicity at doses up to 1000 mg/kg bw/day. This is consistent with the similar observations for other high molecular weight phthalates reviewed by NICNAS (NICNAS, 2007). Effects included transiently decreased body weights, slightly decreased ovary and epididymidal weights, and decreased male and female pup body weights over the weaning period. These effects are considered minor and therefore Di-C7-9 PE is unlikely to affect fertility.

Data from the developmental toxicity tests on Di-C7-9 PE showed no maternal toxicity at doses up to 1000 mg/kg bw/day. The developmental NOAEL was 500 mg/kg bw/day, with a LOAEL based on minor skeletal variations (increased supernumerary lumbar ribs) at 1000 mg/kg bw/day. However, the finding of supernumerary ribs is considered a minor and potentially reversible effect in the absence of other signs of developmental toxicity (NICNAS, 2007). Overall, it can be concluded that Di-C7-9 PE is not likely to affect development.

5. HUMAN HEALTH HAZARD SUMMARY TABLE

<i>Phthalate</i>	<i>Acute Toxicity</i>	<i>Irritation & Sensitisation</i>	<i>Repeated Dose Toxicity</i>	<i>Genetic Toxicity</i>	<i>Carcinogenicity</i>	<i>Fertility</i>	<i>Developmental Toxicity</i>
Di-C7-9 alkyl phthalate (Di-C7-9 PE)	Oral Rat: LD50 >15000 - >20000 mg/kg bw Dermal No data Inhalation No data	Skin irritation: Negative Eye irritation: Negative Respiratory irritation: No data Skin sensitisation: Negative	Rat: NOAEL = 60 mg/kg bw/d LOAEL = 120 mg/kg bw/d, ↓ haemoglobin levels and red blood cell counts and ↑ urinary cell excretion.	No data	No data	NOAEL = 1000 mg/kg bw/d LOAEL = not established	NOAEL = 500 mg/kg bw/d LOAEL = 1000 mg/kg bw/d, ↑ skeletal variations (lumbar ribs)

↑: increase; ↓: decrease

6. REFERENCES

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