Human Health Hazard Assessment

Di-C9-11 alkyl phthalate (Di-C9-11 PE)
(CAS No. 68515-43-5)

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INTRODUCTION

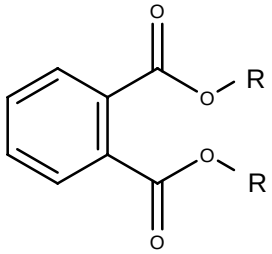
This review of Di-C9-11 alkyl phthalate (Di-C9-11 PE) is a health hazard assessment only. For this assessment, an OECD SIDS Initial Assessment Report on High Molecular Weight Phthalate Esters (HMWPE) (OECD, 2004) was consulted. Information from this report was supplemented with relevant studies from 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 Number:	68515-43-5
Chemical Name:	1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters
Common Name:	Di-C9-11 alkyl phthalate (Di-C9-11 PE)
Molecular Formula:	$C_{28}H_{46}O_4$
Structural Formula:	
	R = C_9H_{19} to $C_{11}H_{23}$ (branched and linear) [>80% linear]
Molecular Weight:	446.7 (based on a di-C10 phthalate ester)
Synonyms:	Di-C9-11 branched and linear alkyl 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	-48°C – -9°C
Boiling point	454°C – 501°C (101.3 kPa)
Density	960 kg/m^3
Vapour pressure	(4.97 – 68.10) x 10^{-10} kPa (25°C)
Water solubility	(<1.70 – 6.10) x 10^{-7} g/L

Partition coefficient n-octanol/water (log Kow)	8.6 – 10.3
Henry's law constant	Not available
Flash point	Not available

Source: OECD (2004)

2. USES

Di-C9-11 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.

Use information in Australia was not available.

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 oral toxicity studies conducted on Di-C9-11 PE, no deaths occurred at doses up to 19700 mg/kg bw, no significant signs of toxicity were noted, and necropsy findings were normal at the end of 14-day observation period. LD50s for the Di-C9-11 PE were:

- >6200 mg/kg bw in rats (BASF AG, 1971*)
- >19700 mg/kg bw in rats and mice (Brown et al., 1970*)

In an intraperitoneal (ip) toxicity study conducted in mice with Di-C9-11 PE, an LD50 > 6200 mg/kg bw was reported (BASF AG, 1971*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C9-11 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-C9-11 PE.

3.3 Irritation

Skin Irritation

Previous Evaluations

In two skin irritation tests, Di-C9-11 PE was not irritating to rabbit skin (Brown et al., 1970*; BASF AG, 1971*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C9-11 PE did not cause skin irritation in rabbits.

Eye Irritation

Previous Evaluations

In two eye irritation tests, Di-C9-11 PE was not irritating to rabbit eyes (Brown et al., 1970*; BASF AG, 1971*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C9-11 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-C9-11 PE (Brown et al., 1970*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C9-11 PE did not induce skin sensitisation in guinea pigs.

3.5 Repeated Dose Toxicity

Previous Evaluations

Oral

In a 7-day gavage study, rats (8/sex) were given Di-C9-11 PE at a dose of 5 mL/kg bw/day (4976 mg/kg bw/d). A control group consisted of 20 rats/sex. The day after the final dose the animals were killed and autopsied. No deaths and no overt signs of toxicity other than a general depression were reported. Histological examination of sections of the major organ tissues revealed periportal cytoplasmic vacuolation in the livers of some rats due to fat deposition (Brown et al., 1970*).

The repeat dose toxicity of Di-C9-11 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 and decreased body weights 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.

The repeat dose toxicity of Di-C9-11 PE was further assessed as part of a developmental study in Sprague-Dawley rats (Fulcher et al., 2001). Groups of 22 timed-mated rats were given 0, 250, 500, or 1000 mg/kg bw/day Di-C7-9 PE daily by oral gavage (5 mL/kg) between gestation days 1 and 19. Control animals received the vehicle alone. Treatment did

not result in any signs of maternal toxicity, and had no statistically significant effects upon litter size, foetal survival or bodyweight. The NOAEL was 1000 mg/kg bw/day (the highest dose tested). The developmental effects are discussed in Section 3.8.

Dermal

Three-week dermal toxicity/irritation studies have been conducted using mixtures containing Di-C9-11 and Di-C7-9 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.

Data not Reported in Previous Evaluations

No data.

Conclusion

In rats, the liver was the main target organ with peroxisome proliferation noted 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. The repeated dose oral NOAEL in rats was 500 mg/kg bw/day, and a LOAEL 1000 mg/kg bw/d based on the toxic effects to the liver (weight and histology).

Di-C9-11 PE and Di-C7-9 PE mixtures did not exhibit any overt toxicity when applied dermally to rabbits and guinea pigs.

3.6 Genetic Toxicity

Previous Evaluations

Di-C9-11 PE was non-mutagenic with and without metabolic activation in the Ames test using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 at concentrations of 20-5000 µg/plate (BASF AG, 1989*).

Data not Reported in Previous Evaluations

No data.

Conclusion

Di-C9-11 PE was negative in bacterial mutation assay. No *in vitro* mammalian mutation, cytogenetic and in vivo genotoxicity data are available for Di-C9-11 PE.

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-C9-11 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). Weight gain was decreased in the first week at all doses in F0 but only in the two highest doses in the F1. Body weight was also reduced through lactation in the high dose group. Liver changes indicative of peroxisome proliferation were noted in both generations and both sexes at the high dose (1.0 %), characterised by increased liver weight in young rats, histopathological changes and decreased weights in mature rats, and an increase in palmitoyl CoA oxidase activity. Relative (not absolute) testes weight was increased in both generations in the 1% group and testicular sperm count was increased in the F0 generation. Relative epididymal weights were decreased in the 1.0% group for F0 (absolute epididymal weights were reduced for both generations), although sperm concentration, motility, and morphology were not affected. There was no impairment of fertility, fecundity, or development in either generation. There was a statistically significant dose-related decrease in male and female F2 (but not F1) pup body weights in the 1.0% group over the weaning period. However, there was no difference in pup weight at birth suggesting that these effects may be due to lactational exposure to Di-C9-11

PE. There was no effect on preputial separation or vaginal opening in the F1 pups. The NOAEL for effects on reproduction was established at 1% (1000 mg/kg bw/day), the highest dose tested and 0.5% (500 mg/kg bw/day) for systemic toxicity based on liver changes. The NOAEL for effects on development was 0.5% (500 mg/kg bw/day) and the LOAEL was 1.0% based on decreased pup weight during weaning.

3.8.2 Developmental toxicity studies

Previous Evaluations

In an OECD standard developmental toxicity study, Di-C9-11 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 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 remarkable macroscopic findings in the maternal animals at necropsy. There were no effects on the incidence of external or visceral abnormalities. An increased incidence of dilated renal pelvis in pups was observed at 1000 mg/kg bw/day with a dose-related trend ($P< 0.01$). Pups of the mid and high dose groups ($\geq$ 500 mg/kg bw/day) also showed increased incidences of supernumerary lumbar ribs (26.7% at high dose compared with 13.6% in controls). The trend was dose-related. 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-C9-11 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 250 mg/kg bw/day. The LOAEL for developmental toxicity was 500 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-C9-11 PE showed no significant reproductive toxicity at doses up to 1000 mg/kg bw/day. Effects included transiently decreased body weights and slightly decreased epididymis weight.

Effects on development

Data from the developmental toxicity tests on Di-C9-11 PE showed no maternal toxicity, at doses up to 1000 mg/kg bw/day. Although no teratogenic effects were seen, increased frequencies of developmental variants including dilated renal pelvis and supernumerary lumbar ribs were produced at and above 500 mg/kg bw/day but they are common findings in rats and thus their toxicological significance is unclear. In the two-generation study, there was a dose-related decrease in male and female F_2 (but not F_1) pup body weights in the 1.0% group over the weaning period. However, there was no difference in pup weight at birth suggesting that these effects may be due to lactational exposure to DiC9-11 PE.

4. HAZARD CHARACTERISATION

Toxicity data for Di-C9-11 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-C9-11 PE.

Di-C9-11 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-C9-11 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-C9-11 PE has low acute oral and intraperitoneal toxicity. No dermal or inhalation toxicity studies are available for Di-C9-11 PE. Based on data for other HMWPEs, Di-C9-11 PE is expected to have low acute dermal and inhalation toxicity (NICNAS, 2007). Di-C9-11 PE did not cause skin or eye irritation or skin sensitisation in animals.

Di-C9-11 PE was negative in Ames test. No *in vitro* mammalian mutation, cytogenetic and in vivo genotoxicity data are available for Di-C9-11 PE. 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 Phthalate Esters Panel HPV Testing Group (2001) and OECD (2004), there is a low likelihood that Di-C9-11 PE is genotoxic.

The primary findings of Di-C9-11 PE in the repeated dose studies were in the liver. Effects of Di-C9-11 PE on the liver included increased palmitoyl PCoA, liver weights, and liver hypertrophy that are indicative of peroxisome proliferation. The repeat dose oral NOAEL in rats was 500 mg/kg bw/day, and a LOAEL 1000 mg/kg bw/d based on the toxic effects to the liver (weight and histology).

No carcinogenicity data are available for Di-C9-11 PE. Due to insufficient testing on other phthalates, it is not possible to extrapolate carcinogenic potential for Di-C9-11 PE.

The multi-generation reproductive toxicity study on Di-C9-11 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 epididymidal weights, and decreased male and female pup body weights over the weaning period. These effects are considered minor and therefore Di-C9-11 PE is unlikely to affect fertility.

Data from the developmental toxicity tests on Di-C9-11 PE showed no maternal toxicity at doses up to 1000 mg/kg bw/day. The developmental NOAEL was 250 mg/kg bw/day, with a LOAEL based on minor skeletal variations (increased supernumerary lumbar ribs) at 500 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-C9-11 PE is not likely to affect development.

5. HUMAN HEALTH HAZARD SUMMARY TABLE

Phthalate	***Acute Toxicity***	***Irritation & Sensitisation***	***Repeated Dose Toxicity***	***Genetic Toxicity***	***Carcinogenicity***	***Fertility***	***Developmental Toxicity***
Di-C9-11 alkyl phthalate (Di-C9-11 PE)	Oral Rat: LD50 >6200 – 19700 mg/kg bw Dermal No data Inhalation No data	Skin irritation: Negative Eye irritation: Negative Respiratory irritation: No data Skin sensitisation: Negative	Rat: NOAEL = 500 mg/kg bw/d LOAEL (2-gen. repro study) = 1000 mg/kg bw/d, ↑ liver weight in young rats, liver histopathological changes and ↓ body weights in mature rats, ↑ in palmitoyl CoA oxidase activity.	*In vitro* Negative in bacterial mutation *In vivo* No data	No data	NOAEL = 1000 mg/kg bw/day LOAEL: not established	NOAEL = 250 mg/kg bw/day LOAEL = 500 mg/kg bw/day, ↑ skeletal variations (lumbar ribs)

↑: increase; ↓: decrease

6. REFERENCES

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