Human Health Hazard Assessment

Dicyclohexyl phthalate (DCHP)
(CAS No. 84-61-7)

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INTRODUCTION

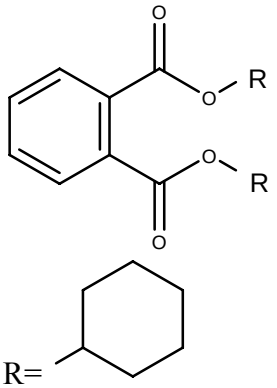
This review of dicyclohexyl phthalate (DCHP) is a health hazard assessment only. For this assessment, primary references were the main source of information, although secondary sources such as a BIBRA Toxicity Profile (BIBRA, 1994) were consulted. The information was updated with relevant studies from 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 reference sources 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 phthalate 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:	84-61-7
Chemical Name:	1, 2-Benzenedicarboxylic acid, dicyclohexyl ester
Common Name:	Dicyclohexyl phthalate (DCHP)
Molecular Formula:	$C_{20}H_{26}O_4$
Structural Formula:	
Molecular Weight:	330.46
Synonyms:	1,2-Benzenedicarboxylic acid, dicyclohexyl ester; Phthalic acid, dicyclohexyl ester; Diclohexyl 1,2-benzenedicarboxylate; Dicyclohexyl phthalate
Purity/Impurities/Additives:	None identified

1.2 Physicochemical Properties

Table 1: Summary of physicochemical properties

Property	***Value***
Physical state	White, crystalline solid
Melting point	66ºC
Boiling point	222ºC-228ºC at 0.5 kPa
Density	1383 kg/m^3 (20ºC)

Vapour pressure	13.3 x 10^{-3} kPa (150ºC)
Water solubility	4 x 10^{-3} g/L (24ºC)
Partition coefficient n-octanol/water (log Kow)	3-4 (temp not specified)
Henry's law constant	No data
Flash point	207ºC

Based on IPCS (1994); HSDB (2002)

2. USES

Dicyclohexyl phthalate (DCHP) is used as a plasticiser (to modify the properties of synthetic resins) for cellulose nitrate, ethyl cellulose, chlorinated rubber, polyvinyl acetate, PVC and other polymers. DCHP is also used as heat sealer for cellulose and in paper finishes (imparts water resistance to printers ink) (HSDB, 2002).

In Australia, DCHP is imported for adhesive manufacture and in screen printing inks. It is also imported for distribution to various institutions and laboratories for research and product development.

3. HUMAN HEALTH HAZARD

3.1 Toxicokinetics

DCHP is hydrolysed *in vitro* by rat, ferret and primate (baboon) liver and intestinal preparations to its corresponding monoester derivative, monocyclohexyl phthalate (MCHP) and cyclohexanol. Hepatic hydrolase activity generally decreased in the order baboon > rat > ferret (Lake et al., 1977). No data were available on absorption or elimination kinetics of DCHP.

Conclusion

There is species similarity in *in vitro* metabolism between rats and primates. DCHP is hydrolysed to its monoester derivative, monocyclohexyl phthalate (MCHP) and cyclohexanol *in vitro*.

3.2 Acute Toxicity

Previous Evaluations

Table 2: Summary of acute toxicity studies

Study	***Species***	***Results (LD_{50}/LC_{50})***	***Reference***
Oral	Rat	30 mL/kg bw (7-day)	HSDB (2002)
	Rat	>3200 mg/kg bw	Eastman Kodak, 1965
	Guinea pig	> 20000 mg/kg bw	Dupont, 1982
	Mouse	> 3200 mg/kg bw	Eastman Kodak, 1965
Dermal	Rabbits	> 300 mg/kg bw	Nuodex, 1979e
Inhalation (1 h)	Rat	> 3.20 mg/L	Nuodex, 1979f
Intraperitoneal	Rat	> 3200 mg/kg bw	Eastman Kodak, 1965
	Mouse	1600 mg/kg bw	Eastman Kodak, 1965

Source: BIBRA (1994)

Data not Reported in Previous Evaluations

No data

Conclusion

DCHP has oral LD50 $_{rat/mouse}$ values >3200 mg/kg bw, a dermal LD50 $_{rabbit}$ value >300 mg/kg bw, inhalation LC50 $_{rat}$ value > 3.20 mg/L and intraperitoneal LD50 $_{rat}$ values >3200 mg/kg bw.

3.3 Irritation

Previous Evaluations

Skin Irritation
Eastman Kodak Co. (1965*) reported that DCHP was a slight skin irritant in guinea pigs. No further information is available.

A 24-hour application of 0.5 g of a preparation containing 15.2% DCHP (other ingredients: n-butyl cyclohexyl phthalate, 61.2%; di-butyl phthalate, 21.9%: di-methyl phthalate, 1.7%) elicited no irritation (no erythema, eschar or oedema formation) to either occluded skin (intact or abraded) of rabbits (6 animals) or guinea pigs (10 animals). The same preparation applied (occluded) for 24-hours over 10 alternate days, caused slight irritation (erythema and oedema) in 40% of guinea pigs after the third application (Nuodex 1979a; 1979b). A mild irritation following repeated 4 hour applications to rabbit skin was noted in a brief translation of an early report (Timofievskaya, 1981*).

Data not Reported in Previous Evaluations

No data.

Conclusion

DCHP in a 15.2% mixture caused mild irritation to guinea pig skin (occluded) but did not cause irritation to either rabbits or guinea pigs skin (occluded). No human skin irritation data are available.

Previous Evaluations

Eye Irritation
Eastman Kodak Co. (1965*) reported that DCHP was a slight irritant, without causing corneal damage, to eyes of rabbits. No further information is available.

Application of 0.1 g of a preparation containing 15.2% DCHP (same formulation as described earlier) caused transient mild irritation to eyes of 6 albino rabbits. Conjunctival redness, chemosis and discharge were the most common observations, which cleared by day 3 after administration (Nuodex, 1979c).

Data not Reported in Previous Evaluations

No data.

Conclusion

DCHP in a 15.2% mixture caused mild irritation to rabbit eyes. No human eye irritation data are available.

3.4 Sensitisation

Previous Evaluations

Skin Sensitisation
Eastman Kodak Co. (1965*) reported that DCHP was not a skin sensitiser in guinea pigs. No further information is available.

In the skin irritation test described in Section 3.3, a preparation containing 15.2% DCHP was applied to guinea pig skin for 24-hour over 10 alternate days (Nuodex, 1979a). After a 2 week rest period, a challenge application for 24 hours was applied to different skin sites. A minimal response (at 24 and 48 hours) was seen in the same four, of 10, guinea pigs that initially reacted to DCHP.

Data not Reported in Previous Evaluations

No data.

Conclusion

DCHP was reported to have minimal or negative responses in skin sensitisation studies. Overall, data are insufficient to determine the skin sensitisation potential of DCHP.

Previous Evaluations

Respiratory Sensitisation

Unspecified exposure to fumes containing DCHP as a major ingredient (>60%) from hot melted adhesives was associated with wheezing in patients upon challenge (Andrasch et al., 1976*; Levy et al., 1978*). However bronchospasm was not induced in a provocation test on a patient with apparent occupationally-induced asthma from exposure to DCHP containing steam during adhesive heating (Pauli et al., 1979*).

Data not Reported in Previous Evaluations

DCHP effects on cell-mediated and humoral immunity were studied in mice (CBA/J strain) spleen cells (*in vitro*) (Yano et al., 2003). DCHP was found to inhibit the secretion of T-helper cell specific cytokines, IFN-γ and IL-4. It was determined that this effect was not mediated through oestrogen receptors.

Conclusion

Data are insufficient to determine the respiratory sensitisation potential of DCHP.

3.5 Repeated Dose Toxicity

Previous Evaluations

Oral

In a 7-day study, young male Sprague-Dawley rats were gavaged with 0, 500, 1000, 1500, 2000 and 2500 mg/kg bw/d DCHP. Total number of animals tested and body weight changes were not reported in this study. It was noted tha results were expressed in groups of 12 or 6 animals. Statistically significant increased relative liver weight was seen at all doses, but no effects on relative weights were seen in testis (except in one animal in the high dose group) or kidney. Histological examinations were confined to tissues from animals receiving 0, 1500 and 2500 doses. Examination of the liver revealed slight hypertrophy of centrilobular cells at 1500 mg/kg bw/d, which was more marked at 2500 mg/kg bw/d. One animal in the high dose group had bilateral testicular atrophy. Ultrastructural examination revealed marked proliferation of endoplasmic reticulum of centrilobular cells at and above 1500 mg/kg bw/d. No evidence of peroxisome proliferation was observed (Lake et al, 1982). A LOAEL of 500 mg/kg bw/d was determined based on increased relative liver weights.

In a 21-day gavage study, liver enlargement, stomach abnormalities (squamous cell hyperplasia) and testicular atrophy were seen in rats administered 4170 mg/kg bw/d DCHP (Grasso, 1978*). No other details were provided.

In a 90-day study in rats, liver weight changes but no tissue abnormalities were seen at doses of DCHP at 200 mg/kg bw/d (de Ryke & Willems, 1977*).

No effects were reported in rats dosed by gavage with 200 mg/kg bw/d DCHP (25% in olive oil), twice a week for 6 weeks and 1 year (Bornmann, 1956*). NOAEL with values ranging from 1 and 27 mg/kg bw/d, were also reported in rat studies of duration up to 2 years. No further information is available (Bornmann, 1956*).

A NOAEL of 14 mg/kg bw/d was reported in dogs in a one-year feeding study. No further information is available (Shibko and Blumenthal, 1973*).

The DCHP metabolites, monocyclohexyl phthalate (MCHP) and cyclohexanol, were administered separately to Sprague-Dawley rats over 7 days at 1130 mg/kg bw/d and 455 mg/kg bw/d respectively (doses equimolar to 1500 mg/kg bw/d DCHP). Significantly increased in relative liver weights but not relative kidney weight were induced with both metabolites. Induction of hepatic xenobiotic metabolism was also observed. MCPH, but not cyclohexanol, also resulted in a marked reduction in relative weight of testes, (to 44% of control values) with bilateral atrophy of the germinal epithelium of seminiferous tubules observed histologically. The greater potency of MCHP compared to DCHP was attributed to greater absorption within the gastrointestinal tract (Lake et al, 1982).

Data not Reported in Previous Evaluations

Sprague Dawley rats were fed a diet containing 0, 240, 1200 or 6000 ppm DCHP in a 2-generation reproductive toxicity study. Effects included decreased food consumption and body weight gain, hypertrophy of hepatocytes, focal seminiferous tubule atrophy were observed in both sexes at 1200 ppm (80-107 mg/kg bw/d; m-f) and 6000 ppm (402-534 mg/kg bw/d; m-f). At 6000 ppm, increased liver and thyroid weight, decreased relative prostate weight, increased hyaline droplets in renal tissue were observed only in male rats (Hoshino et al., 2005) (also see 3.8.2 Two-Generation reproductive toxicity studies).

Conclusion

Limited data are available on repeat dose toxicity for DCHP. Based on a 7-day gavage rat study, the liver appears to be the primary target organ, with effects seen in the centrilobular region. A LOAEL of 500 mg/kg bw/d was determined based on increased relative liver weights. A NOAEL was not established.

3.6 Genetic Toxicity

Previous Evaluations

A preparation containing DCHP (15.2%) was not genotoxic in bacterial DNA repair and mutation tests in *E. coli,* both with and without exogenous metabolic activation (Nuodex, 1979d*).

DCHP also gave negative results for mutagenic potential in an Ames test using *S. typhimurium,* both with and without metabolic activation (Zeiger et al., 1985*).

No *in vivo* data are available.

Data not Reported in Previous Evaluations

No data.

Conclusion

DCHP in a mixture was negative in bacterial mutation and DNA damage assays, both with and without exogenous metabolic activation.

No other *in vitro* or *in vivo* genotoxicity studies are available. Overall, the genotoxic potential of DCHP cannot be determined.

3.7 Carcinogenicity

Previous Evaluations

No *in vivo* carcinogenicity studies in animals have been undertaken for DCHP. In addition, no human data are available.

A phthalate ester mixture containing 15.2% DCHP was tested in an *in vitro* mammalian C3H/10T$^{1}/_{2}$ cell transformation assay. The mixture did not induce cell transformation at doses ranging from 0.0195 to 0.0025 µl/ml (Nuodex, 1982).

In a 21-day gavage study, squamous cell hyperplasia in the stomach was seen in rats given 4170 mg/kg bw/d DCHP. No further details were provided. (Grasso, 1978*).

Carcinogenic effects were not observed in an 18-month, 4-generation dietary study in Wistar rats, administered DCHP in diet at concentrations of 100 mg/kg feed (highest estimated dose of 5 mg/kg bw/d) (Lefaux, 1968*).

Data not Reported in Previous Evaluations

No data.

Conclusion

A mixture containing DCHP tested negative in an *in vitro* mammalian cell transformation assay.

A short-term dosing (21 day) study reported squamous cell hyperplasia in the stomach of rats with DCHP. No pre-neoplastic or neoplastic lesions were observed in an 18-month, 4-generation dietary study in Wistar rats.

Overall, data are insufficient to draw any conclusions with regard to the carcinogenic potential of DCHP.

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 animals 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. Studies include repeat dose toxicity studies that dose adult animals for varying duration and two-generation studies. The effects on fertility (as adults) and development (as foetuses) will then be discussed separately.

3.8.1 Repeat dose toxicity studies

Previous Evaluations

Testicular atrophy was reported by Grasso (1978*) in rats gavaged with 4.2 g/kg bw/d DCHP for 21 days. In rats administered with 1.5 g/kg bw/d for 7 days, MCPH (the main metabolite of DCHP) caused increased liver weight as well as testicular effects, notably reduced testis weight, cellular abnormalities and atrophy (Lake et al, 1982).

3.8.2 Two-Generation reproductive toxicity studies

Previous Evaluations

No effects on fertility, parturition or nursing were reported in a 4-generation feeding study in rats administered 100 mg DCHP/kg feed (estimated high dose of 5 mg/kg bw/d) for 18 months. A detailed examination of foetuses/pups was apparently not undertaken in this study (Lefaux, 1968*).

A group of eight female rats given 2 ml of a 25% solution (0.6 g/kg bw/day) for 6 weeks and then mated to untreated males showed no difference in litter size. Development, growth and fertility of three subsequent (untreated and inbred) generations were also similarly unaffected (Bornmann et al., 1956*).

Data not Reported in Previous Evaluations

In a two-generation study, Sprague Dawley rats were fed a diet containing 0, 240, 1200 or 6000 ppm DCHP (Hoshino et al., 2005). Parental effects included decreased food consumption and body weight gain, hypertrophy of hepatocytes, focal seminiferous tubule atrophy and decreased sperm head counts (F_1 only) at the two highest doses. At 6000 ppm, effects included increased liver and thyroid weight, decreased relative prostate weight, increased hyaline droplets in renal tissue (F_0 and F_1 males only), decreased prostate weight (F_1 only) and diffuse and/or focal atrophy of the seminiferous tubules (F_1 only). There were no effects on reproductive endpoints such as fertility, mating, gestation and birth index.

Among offspring there was decreased body weight gain in F_1 and F_2 at the highest dose; decreased anogenital distance and retained thoracic nipples in F_1 males at 6000 ppm and F_2 males at 1200 ppm and 6000 ppm but no effect on timing of sexual maturation. The effects on nipple retention were more severe in the F_2 compared with F_1 generation (more offspring retained areolae). The decrease in anogenital distance was significantly different than controls at a lower dose in F_2 (1200 ppm) compared to F_1 generation (6000 ppm). The NOAEL for fertility was 240 ppm (16-21 mg/kg bw/day; m-f) based on decreased sperm head counts and focal seminiferous tubule atrophy in F_1 males at 1200 ppm (80-107 mg/kg bw/day; m-f). The maternal NOAEL was 240 ppm based on changes in body and liver weights at 1200 ppm. For developmental effects, the NOAEL was 240 ppm (16-21 mg/kg bw/day; m-f), and LOAEL was 1200 ppm (80-107 mg/kg bw/day; m-f) based on decreased anogenital distance and retained nipples in F_2 males.

3.8.3 Mode of action

DCHP has been shown to bind to human oestrogenic receptor *in vitro* (Nakai et al., 1999). DCHP binding was biphasic and was three orders of magnitude weaker than 17β-oestradiol (Nakai et al., 1999). DCHP possessed oestrogenic activity in some *in vitro* assays (Okubo et al., 2003; Hong et al., 2005) but was negative in other assays (yeast two-hybrid assay, Nishihara et al., 2000; estrogen receptor-α reporter gene, Yamasaki et al., 2002). DCHP was also negative in the reporter gene assay for ERα-mediated transcriptional activation (up to 10 μM) and *in vivo* uterotrophic assays (0, 2, 20 and 200 mg/kg). DCHP elicited an oestrogen-like non-receptor mediated inhibitory effect on nicotinic acetylcholine receptor-coupled calcium response in bovine adrenal and human neuroblastoma cells. DCHP was approximately 2 times more potent than 17α-oestradiol in bovine adrenal cells and 10-fold more potent in human neuroblastoma cells (Liu & Lin, 2002; Lu et al., 2004). DCHP (but not MCHP) increased proliferation of human breast cancer MCF-7 cells (Okubo et al., 2003; Hong et al., 2005). However, the effects were not replicated *in vivo* as oral treatment with 600 mg/kg bw/day DCHP for 3 days did not increase expression of CaBP-9k mRNA in 7 day old female SD rats, a gene highly regulated by 17β-oestradiol (Hong et al., 2005). Subcutaneous injection of DCHP doses up to 200 mg/kg bw/day for 3 days was not uterotrophic (Yamasaki et al., 2002).

MCHP suppressed (displayed anti-oestrogenic activity) the stimulatory effect of 17β-oestradiol on proliferation of MCF-7 cells *in vitro* (Okubo et al., 2003). One proposed mode of action of oestrogen induced reproductive effects is an effect on cell differentiation/transformation. For many oestrogens, this mode of action is characterised by disruption of the microtubule network and aneuploidy induction. DCHP showed no disruptive activity on the microtubule network *in vitro* in Chinese hamster V79 cells (up to 200 μM) or *in vivo* (up to 500 mg/kg) in rat Sertoli cells (Nakagomi et al., 2001).

Conclusion

Effects on Fertility

There were minor reproductive effects in a well-performed two-generation study in rats. The NOAEL for fertility 240 ppm (16-21 mg/kg bw/day) based on decreased sperm head counts and focal seminiferous tubule atrophy in F_1 males at 1200 ppm (80-107 mg/kg bw/day). There were no effects on reproductive endpoints such as fertility, mating, gestation and birth index. At higher doses (in poorly described studies), testicular atrophy has been reported for DCHP (4.2 g/kg bw/d for 21 days) and MCHP (1.5 g/kg bw/d for 7 days).

Developmental Effects
DCHP was tested in a well-performed two-generation study in rats. The NOAEL for developmental effects is 240 ppm (16-21 mg/kg bw/day) based on decreased anogenital distance and retained nipples in F_2 males at 1200 ppm (80-107mg/kg bw/day). These effects occurred at doses that were associated with decreased maternal food consumption, final body weight and increased liver weight. The developmental effects were more severe and occurred at a lower dose in the F_2 compared with F_1 generation.

4. HAZARD CHARACTERISATION

Toxicity data for DCHP 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 (NICNAS, 2007), which contains a comparative analysis of toxicity endpoints across 25 phthalates, including DCHP.

DCHP is a phthalate with a sidechain ring structure. It does not possess simple straight or branched carbon sudechains as many other typical phthalates, however, it can be considered to belong to a group of "transitional" phthalates defined as those produced from alcohols with straight-chain carbon backbones of C4-6 (NICNAS, 2007).

DCHP has oral $LD50_{rat}$ values >3200 mg/kg bw, a dermal $LD50_{rabbit}$ value >300 mg/kg bw, a inhalation $LC50_{rat}$ value > 3.20 mg/L and intraperitoneal $LD50_{rat}$ values >3200 mg/kg bw. Similar to other phthalates reviewed (NICNAS, 2007), DCHP can be considered to have low acute toxicity.

A phthalate mixture containing 15.2% DCHP was a mild eye irritant in rabbits and a mild skin irritant in guinea pigs. No human data were available. On the basis of information from phthalates of similar molecular weight, DCHP is likely to produce minimal skin and eye irritant effects. There is insufficient data to determine the sensitisation potential of DCHP.

In limited repeat dose studies in rats, the liver was the primary target organ (increased relative liver weights and centrilobular changes), with effects also seen in stomach, adrenal glands and spleen. Similar effects on the liver in addition to reductions in testes weights were also seen with the DCHP metabolites, monocyclohexyl phthalate and cyclohexanol. No kidney effects were reported, except from a study where rats consumed a diet of plastic film containing ingredients including DCHP reporting focal desquamation of kidney tubule epithelium. No effects on peroxisome proliferation were seen in a 7-day study at doses up to 2500 mg/kg bw/d DCHP. The LOAEL, reported in a 7-day study study, was 500 mg/kg bw/d, based on increases in relative liver weight. A NOAEL could not be determined from the available data.

In a two-generation study, non-reproductive effects included decreased food consumption and body weight gain, hypertrophy of hepatocytes, focal seminiferous tubule atrophy were observed in rats at 1200 ppm (80-107 mg/kg bw/d; m-f) and 6000 ppm (402-534 mg/kg bw/d; m-f). At 6000 ppm, increased liver and thyroid weight, decreased relative prostate weight, increased hyaline droplets in renal tissue were observed only in male rats.

DCHP was negative in *in vitro* mutagenic (with or without metabolic activation) and cell transformation assays. No *in vitro* cytogenetic and *in vivo* genotoxicity studies are available for assessment. Data are insufficient to determine the genotoxic potential of DCHP.

No carcinogenicity studies were available for assessment. Increases in liver weight and squamous cell hyperplasia of the stomach were reported in sub-acute studies, however the significance of these effects for carcinogenic potential is not known.

In the same two-generation study, no effects on reproductive endpoints such as fertility, mating, gestation and birth index, however, sperm head counts and focal seminiferous tubule atrophy were observed at 1200 ppm (80-107 mg/kg bw/day; m-f) in F_1 males. The NOAEL was 240 ppm (16-21 mg/kg bw/day; m-f). In another poorly described studies, testicular atrophy has been reported for DCHP (4.2 g/kg bw/d for 21 days) and MCHP (1.1 g/kg bw/d for 7 days).

Developmental effects (decreased anogenital distance and retained nipples) were observed in F_1 and F_2 offspring. Maternal effects were minor at these doses (decreased maternal food consumption, final body weight and increased liver weight). The developmental effects were more severe and occurred at a lower dose in the F_2 compared with F_1 generation. The NOAEL for developmental effects was 240 ppm (16-21 mg/kg bw/day) based on decreased anogenital distance and retained nipples in F_2 males at 1200 ppm (80-107 mg/kg bw/day).

Although data for DCHP are limited, the fertility and developmental effects observed are similar to those phthalates with sidechain backbone of 4-6 carbon atoms in length (C4-6) (NICNAS, 2007). These C4-6 phthalates previously referred to as ‘transitional’ phthalates (Phthalate Esters Panel HPV Testing Group, 2001) have also been associated with male reproductive (seminiferous tubule atrophy) and developmental (decreased anogenital distance and retention of nipples) effects. Overall, DCHP has a similar reproductive toxicity profile to ‘transitional’ (C4-6) phthalates for which reproductive and developmental effects are recognised.

5. HUMAN HEALTH HAZARD SUMMARY TABLE

Phthalate	***Acute Toxicity***	***Irritation & Sensitisation***	***Repeated Dose Toxicity***	***Genetic Toxicity***	***Carcinogenicity***	***Fertility***	***Developmental Toxicity***
Dicyclohexyl phthalate (DCHP)	Oral Rat/mouse: LD50 >3200 mg/kg bw Dermal Rabbit: LD50 >300 mg/kg bw Inhalation Rat: LC50 >3.20 mg/L Intraperitoneal Rat: LD50 >3200 mg/kg bw	Skin Irritation: minimal effects Eye Irritation: minimal effects Skin sensitisation: insufficient data	Rat (7 days): NOAEL = not established LOAEL = 500 mg/kg bw/d ↑ relative liver weights High doses: liver and testes effects. No PP noted.	*In vitro* Negative in bacterial mutation assays *In vivo* No data	Insufficient data	*Two generation study* Rat: NOAEL = 240 ppm (16-21 mg/kg bw/d, m-f) LOAEL = 1200 ppm (80-107 mg/kg bw/d, m-f); based on ↓ sperm head counts and focal seminiferous tubule atrophy in F1 males	*Two generation study* Rat: NOAEL = 240 ppm (16-21 mg/kg bw/d, m-f) LOAEL =200 ppm (80-107 mg/kg bw/d, m-f); ↓ anogenital distance & retained nipples in F2 males

PP: peroxisome proliferation; m-f: male-female; ↑: increase; ↓: decrease.

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7. ROBUST STUDY SUMMARIES

Test Substance	:	DCHP
Type of Test	:	Two generation Reproductive Toxicity
Species	:	Rats, Sprague Dawley, 24/M/F, 5 weeks, weight unknown. Asutagi breeding centre.
Route of admin.	:	Diet
Study Duration	:	Two generations
Frequency of treatment	:	Ad libitum
Post exposure period	:	None
Doses	:	0, 240, 1200, 6000 ppm (0, 16-21, 80-107, 402-534 mg/kg bw/d; m-f)
Control group	:	unadulterated diet (NIH-07M)
NOAEL / NOEL	:	Fertility: 240 ppm (16-21 mg/kg bw/d, m-f) Devp: 240 ppm (16-21 mg/kg bw/d, m-f)
LOAEL / LOEL	:	Fertility: 1200 ppm (80-107 mg/kg bw/d, m-f) Devp: 1200 ppm (80-107 mg/kg bw/d, m-f)
GLP& QA	:	No data
Guidelines	:	OECD guideline No. 416.
Method	:	Rats were fed diet for 10 weeks prior to mating to necroscopy (end of mating period: males; mating, gestation and lactation: females). Administration to F_1 started at weaning and continued to necroscopy (as per F_0). Sperm motility was tested in 10 F_0 and F_1 males. Hormone measurement (testosterone, FSH, estradiol, LH) of 6 male and female F_0 and F_1 parents were taken at necroscopy. Histological examination from all male and female F_0 and F_1 parents was conducted. Body weight, anogenital distance (on PND 4) and presence of areolae (PND 12-14) were taken.
Result	:	Parental effects included decreased food consumption (F_0 females, F_1 males) and final body weight at the two highest doses, focal seminiferous tubule atrophy, hypertrophy of hepatocytes and decreased sperm head counts (F_1 only) at the two highest doses. At 6000 ppm, effects included increased liver and thyroid weight, decreased relative prostate weight (F_1 only), increased hyaline droplets in renal tissue (F_0 and F_1 males only), decreased prostate weight (F_1 only) and diffuse and/or focal atrophy of the seminiferous tubules (F_1 only). There were no effects on reproductive endpoints such as fertility, mating, gestation and birth index, however, sperm head counts and focal seminiferous tubule atrophy were observed at 1200 ppm. Among offspring there was decreased body weight gain in F_1 and F_2 at the highest dose; decreased anogenital distance and retained thoracic nipples in F_1 males at 6000 ppm and F_2 males at 1200 ppm and 6000 ppm.
Conclusion	:	Results suggested DCHP to be a developmental toxicant.
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