Human Health Hazard Assessment

Dimethyl phthalate (DMP)
(CAS No. 131-11-3)

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INTRODUCTION

This review of dimethyl phthalate (DMP) is a health hazard assessment only. For this assessment, a review by Cosmetic Ingredient Review (CIR, 2002) was the main source of information. Information was also obtained from BIBRA (1994) and from the European Chemicals Bureau IUCLID Dataset on DMP (ECB, 2000). The IUCLID dataset has not undergone evaluation by the European Commission. These information sources were supplemented with relevant studies from more recent literature surveys conducted up to September 2006.

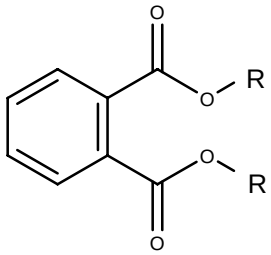
References not marked with an asterisk were examined for the purposes of this assessment. References not examined but quoted from the key reviews as secondary citations are also noted in this assessment and marked with an asterisk.

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: 131-11-3
Chemical Name: 1,2-Benzenedicarboxylic acid, dimethyl ester
Common Name: Dimethyl phthalate (DMP)
Molecular Formula: $C_{10}H_{10}O_4$
Structural Formula:



R = $-CH_3$

Molecular Weight: 194.19
Synonyms: Dimethyl-1,2-benzenedicarboxylate, Phthalic acid dimethyl ester, Dimethyl benzeneorthodicarboxylate, Dimethyl o-phthalate
Purity/Impurities/Additives: None identified

1.2 Physico-Chemical Properties

Table 1: Summary of physico-chemical properties

Property	***Value***
Physical state	Colourless oily liquid
Melting point	5.5°C
Boiling point	284°C
Density	1190 kg/m^3 (20°C)

Vapour pressure	8.0×10^{-4} (20°C)
Water solubility	4.3 g/L (20°C)
Partition coefficient n-octanol/water (log Kow)	1.47 - 2.12 (temperature not specified)
Henry's law constant	Not available
Flash point	146°C

Source: ECB (2000), IPCS (2005)

2. USES

Internationally, DMP is used in cosmetics as a fragrance ingredient, solvent and plasticiser (CIR, 2002). DMP is an ingredient in hair sprays, conditioners and rinses, face powders and foundations, bath soaps and detergents, deodorants and aftershave lotions. Non-cosmetic uses include as solvents and plasticisers for nitrocellulose, cellulose acetate and cellulose acetate-butyrate compositions. DMP is used as a fabric treatment, in explosives, safety glass, printing inks, paper coatings and adhesives and also in insecticides and insect repellents (CIR, 2002).

In Australia, DMP is imported as finished products or mixtures and as a raw chemical for local manufacture. The chemical is used industrially for automotive parts, encapsulation of electrical wiring, mining and construction (e.g. minerals separation chemicals, insulation coatings and specialised surface protection coatings such as on aluminium extrusions) and fabrication of fibreglass, paints, nitrocellulose, cellulose acetates and rubber. Downstream products include plastic articles, children's toys, fragrances bases for household cleaning and cosmetic products, adhesives, putty hardeners, paints and coatings. DMP is also distributed to various institutions and laboratories for biotechnological and pharmaceutical research.

3. HUMAN HEALTH HAZARD

3.1 Toxicokinetics

Previous Evaluations

The following data are obtained from CIR (2002).

DMP is readily absorbed from the gastrointestinal system primarily as the monoester (White et al., 1980*). It is also absorbed via skin. Following absorption in the rat, DMP is distributed to a variety of tissues and excreted with little retained. In rats, a relatively constant 6% of an applied dermal dose of DMP was recovered in the urine and faeces per day over 7 days (Elsisi et al., 1989). After 7 days, up to 40% of the dose was recovered from urine and faeces with 19% remaining at the dose site (Elsisi et al., 1989).

In vitro studies (Scott et al., 1987; Hilton et al., 1994) provided values of 2.5 to 4 μg/cm^2/h for absorption of DMP through human epidermis and 40 to 50 μg/cm^2/h through rat epidermis. Dermal absorption of DMP in rat was highly solvent dependent, with up to a 10-fold difference between different solvents. Solvent effects were not as pronounced in human skin (Hilton et al., 1994). Reifenrath et al. (1989*) reported a peak rate of 3 μg/cm^2/h for pig skin.

Following oral administration in rats, the primary metabolites for DMP in urine were the monoester monomethyl phthalate (MMP) (78%) with some free phthalic acid (14.4%) and unchanged DMP (8.1%) (Albro & Moore, 1974*). *In vitro*, the rate of metabolism of DMP by rat epidermal homogenates was approximately 1.5% that of liver homogenates (Kozumbo

et al., 1982*). Methanol and formaldehyde have been reported as *in vivo* and *in vitro* metabolites of DMP (Kozumbo & Rubin, 1991*; Surina et al, 1984*).

Data not Reported in Previous Evaluations

No data.

Conclusion

DMP is absorbed via the gastrointestinal tract and via skin. In rats, 6% per day of dermally applied DMP was recovered in urine and faeces over 7 days. *In vitro,* human epidermis was an order of magnitude less permeable to DMP than rat epidermis. Following absorption, DMP is distributed to multiple organs but rapidly cleared, with no accumulation.

Following oral administration, the main DMP metabolites were the monoester (MMP) (78%), with free phthalic acid and unchanged DMP comprising the remainder of the eliminated dose. Methanol and formaldehyde have also been identified as metabolites *in vivo* and *in vitro*.

3.2 Acute Toxicity

Previous Evaluations

Table 2. Acute toxicity studies

Study	***Species***	***Results (LD50/LC50)***	***References***
Oral	Rat	6.9 ml/kg bw (8.2 g/kg bw)[#]	Draize et al. (1948)*
	Rabbit	4.4 ml/kg bw (5.2 g/kg bw)[#]	Draize et al. (1948)*
	Guinea pig	2.4 ml/kg bw (2.9 g/kg bw)[#]	Draize et al. (1948)*
	Chick	8.5 ml/kg bw (10.1 g/kg bw)[#]	Draize et al. (1948)*
	Mouse	7.2 ml/kg bw (8.6 g/kg bw)[#]	Draize et al. (1948)*
	Mouse	6.3 g/kg bw	Plasterer et al. (1985)
Intraperitoneal	Mouse	18.8 mmol/kg bw (3.7 g/kg bw)[#]	Karel et al. (1947)*
	Mouse	3.98 g/kg bw	Lawrence et al. (1975)*
	Rat	3.38 ml/kg bw (4.0 g/kg bw)[#]	Singh et al. (1972)

Source: CIR (2002); [#] - calculated

In addition to the above data from CIR (2002), the IUCLID for DMP contains a compilation of summarised acute toxicity data not evaluated by the European Commission (ECB, 2000). In the only study noted as being conducted to Good Laboratory Practice (GLP), the oral LD50 for DMP in rats was 5740 mg/kg bw for males and 4390 mg/kg bw for females (Union Carbide Corp, 1987*). Dermal LD50 values noted by ECB (2000) range from > 4800 mg/kg bw in guinea pigs to 38000 mg/kg bw in rats.

No deaths resulted in rats (number unspecified) from acute inhalation of a saturated vapour (no details of concentration) of DMP for 6 hours a day (Levinskas, 1973*). Cats survived a 6.5 hour exposure to a DMP mist of 2.0 mg/L but one of two cats died when the concentration was increased to 10.2 mg/L (Levinskas, 1973*).

Data not Reported in Previous Evaluations

No additional data were available.

Conclusion

DMP is of low acute oral and dermal toxicity. The oral LD50 was 4390-8200 mg/kg bw/d (rats) and the dermal LD50 was 38000 mg/kg bw (rats) and > 4800 mg/kg bw (guinea pigs). Data are insufficient to determine the potential for acute inhalation toxicity.

3.3 Irritation

Skin Irritation

Previous Evaluations

Irritation and ulceration were reported from a one-year dermal initiation/promotion study following daily application of 0.1 ml of DMP to unoccluded mouse skin (5 days per week) (NTP, 1995). However, the effects of vehicle could not be discounted in this study design.

DMP was reported as not irritating in rabbits in a Draize test following application of up to 4 ml/kg bw to occluded and unoccluded (intact and abraded) skin (Draize et al., 1948*). DMP was not irritating except in molting areas with 0.5 ml applied to clipped, intact and abraded skin of 3 rabbits for 24 hours (Lehman, 1955).

No skin irritation was reported when DMP was applied at doses up to 4.0 ml/kg per day for 90 days to the clipped intact skin of rabbits. However, DMP was irritating to the penile mucosa (Lehman, 1955). No significant irritation was reported in another short-term dermal study of 25 applications of 4.8 g/kg bw/d for 33 days under occlusion (Dow Chemical, 1946*).

Dupont (1970*) reported that 0.05 ml DMP applied to intact skin of male albino guinea pigs produced no primary irritation. Also, 9 similar applications of DMP to abraded skin in guinea pigs over a 3 week period produced no oedema or erythema (Dupont, 1970)*.

Human studies

Closed patch tests provoked irritant reactions in 3 of 190 subjects (equivocal in a further 6) tested with 0.5% DMP in a cream base (Takenaka et al., 1970*). In another study, application of 50% DMP (in ethanol) to the face of 10 volunteers produced no visible signs of irritation (Frosch & Kligman, 1977*). No further details were provided for these studies.

Data not Reported in Previous Evaluations

No data.

Conclusion

None of the studies were conducted according to recognised guidelines. Available data suggests DMP causes minimal skin irritation in rabbits and guinea pigs. Similar minimal effects are suggested in humans.

Eye Irritation

Previous Evaluations

Application of up to 0.5 ml of undiluted DMP to the rabbit eye produced, at most, slight irritation (Draize et al., 1944*; Carpenter & Smyth, 1946*; Lawrence et al., 1975*).

Human studies

McLaughlin (1946)* reported that human contact with undiluted DMP produced corneal damage, which following medical treatment healed within 48 hours with no loss of vision. No further details were provided.

Data not Reported in Previous Evaluations

No data.

Conclusion

None of the studies were conducted according to recognised guidelines. Limited data suggest DMP induces minimal eye irritation in rabbits. A single case report suggested DMP may induce eye irritation in humans.

Respiratory Irritation

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

3.4 Sensitisation

Previous Evaluations

No evidence of sensitisation was seen in rabbits receiving daily skin applications of DMP at doses of up to 4 ml/kg per day for 90 days (Lehman, 1955).

No signs of oedema or erythema were seen in guinea pigs when challenged with DMP on abraded or intact skin, 2 weeks after a 3-week period of 9 dermal applications of 0.05 ml DMP (Dupont, 1970*).

Human studies

Only one positive reaction was observed in 1532 dermatitis patients patch tested (48 hours under a "closed" patch) with a mixture of 2% DMP, 2% DEP and 2% DBP in petrolatum (Schulsiner & Mollgaard, 1980*). A positive patch test response to DMP (5% in petrolatum) was reported in a 71-year old woman (with contact dermatitis) in a separate case report (Oliwiecki et al., 1991*).

Patch testing of 16 subjects (8 per sex) did not reveal any positive responses to DMP when challenged for 2 days following a 2-week 'rest period' after 6 days of continuous dermal application (Dupont, 1982*).

Kanerva et al. (1999) reported results from patch testing of patients referred to an occupational dermatology clinic over a 6 year period. None out of 310 patients tested with 5% DMP under occlusion for 2 days exhibited allergic reactions.

Data not Reported in Previous Evaluations

No data.

Conclusion

Available animal and human studies indicate that DMP does not cause skin sensitisation.

3.5 Repeated Dose Toxicity

Previous Evaluations

Oral

In a 4-day Sprague-Dawley rat study, administration (by gavage) of 1400 mg/kg bw/d DMP induced no significant changes in body weight, testes weight, testes microscopic appearance or in urinary zinc excretion (Cater et al., 1977*; Foster et al., 1980*; Gangolli, 1982*).

DMP administered in diet at 2% (approximately 2000 mg/kg bw/d) to 10 young male JCL:Wistar rats for 7 days, induced statistically significant elevations in liver weights (approx. 17%) compared to 20 control animals (Oishi & Hiraga, 1980). Zinc levels in the liver and testes were unaffected, but the concentration of testosterone in the serum and testes was decreased by approximately 50 to 70%.

In 14-day (gavage) and 21-day (feeding) studies, DMP at doses of 1000 and 500 mg/kg bw/d, respectively, did not induce hepatomegaly in rats (Lake et al., 1978*; Bell et al., 1978*). In the 21-day study in Sprague-Dawley rats, no effects on growth or liver weight were reported. Reductions in cholesterol and total lipids were reported in liver, but not in serum (ECB 2000).

In a 2-year rat study (10 females/dose), DMP in the diet at 2, 4 and 8% (approximately 1000, 2000 and 4000 mg/kg bw/d) induced chronic nephritis in the high dose group. Exposure to 4% and 8% had a slight but significant effect on growth. A NOAEL of 1000 mg/kg bw/d was determined for this study based on reduced body weight gain at 2000 mg/kg bw/d (Lehman, 1955).

Dermal

A slight reduction in haematocrit and testes weights were reported in rabbits following dermal application of DMP (4800 mg/kg bw day for 33 days). No histological changes were seen at termination (Dow Chemical, 1946*).

In a 3-month rat (males only) study (application doses of 200, 1250, 2000 mg/kg bw/d), nervous system and renal function changes were noted at 1250 and 2000 mg/kg bw/d (Timofievskaya et al., 1976*).

In a 90-day (dermal) study in rabbits, daily DMP applications of 600-4800 mg/kg bw/d produced slight renal damage (nephritis) at 2400 mg/kg bw/d, weight loss, pulmonary oedema and kidney and liver damage at 4800 mg/kg bw/d. A NOAEL of 1200 mg/kg bw/d was determined for this study, based on nephritis seen at 2400 mg/kg bw/d and above (Draize et al., 1944*; 1948*; Lehman, 1955).

In a one-year carcinogenicity study (see section 3.7), no gross or histopathologic changes or changes in body weight or survival indices were reported in male Swiss CD-1 mice following 5 applications per week of 0.1 ml DMP (~3000 mg/kg bw) (NTP, 1995).

Inhalation

In a 4-month rat study, exposure to concentrations of 0.68 and 1.84 mg/m^3 DMP for 4 hours/d resulted in changes in respiratory rate, decreased haemoglobin, altered red blood cell count, reduced weight gain, disturbed diuresis, altered chloride in urine and increased clearance of hippuric acid at the high dose (Timofievskaya et al., 1974*).

Data not Reported in Previous Evaluations

No additional data were available.

Conclusion

In general, limited data are available from repeat dose studies of DMP in animals. In oral studies in rats, high doses (above 2000 mg/kg bw/d) induced kidney effects (nephritis) and liver effects (weight increases). The highest doses (4800 mg/kg bw/d) induced weight loss, pulmonary oedema and kidney and liver damage. In separate studies, increases in liver weight and decreases in liver cholesterol and total lipids were reported.

From a limited 2-year rat oral feeding study, a NOAEL of 1000 mg/kg bw/d was reported. The LOAEL was 2000 mg/kg bw/d based on reduced body weight gains.

A single available study of inhalation exposure was inadequate to establish conclusions on repeated inhalation toxicity.

In repeat dose dermal studies in rats and rabbits, the kidney appears to be the primary target organ with effects on nervous system (rat), lungs and testes (rabbit) also reported. The sub-chronic repeat dose (dermal) NOAEL in rabbits from a 90-day study was reported as 1200 mg/kg bw/d, based on nephritis seen at 2400 mg/kg bw/d and above.

3.6 Genetic Toxicity

Previous Evaluations

In vitro

In a modified Ames test (with histidine and biotin incorporation), DMP produced a positive dose-related (500 to 4000 μg/plate) mutagenic response in *S. typhimurium* strain TA100 without metabolic activiation, but negative with and without metabolic activation with *S. typhimurium* strain TA98 (Kozumbo et al., 1982). DMP was also tested by Agarwal et al (1985) in *S. typhimurium* strains TA98, TA100, TA1535, 1537, 1538 and 2637, up to 2000 μg/plate, both with and without metabolic activation. DMP produced a significant increase in

TA1535 revertant colonies at 500-750 μg/plate. This effect was eliminated when S9 was added to the mix.

In a liquid suspension assay (measuring 8-azaguanine resistance), DMP was weakly positive in *S. typhimurium* strains TA 100 without metabolic activation. A dose-related increase in revertant frequency (mutagenic response) was seen from 5 to 10 mM DMP. Increasing the concentration of S9 by five-fold completely blocked the mutagenic response (Seed, 1982).

NTP (1995) reported that DMP (33-6,666 μg/plate) was negative in *S. typhimurium* strains TA98, 100, 1535, and 1537 both with and without metabolic activation. Neither MMP (main *in vitro* metabolite) nor rat urine (from animals treated by ip injection of 0.02 μg /kg DMP) were mutagenic in Ames or *E. coli* mutation assays (Kozumbo & Rubin, 1991).

DMP induced sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells, only with metabolic activation, but did not induce chromosome aberrations (NTP 1995). Similarly, DMP at doses up to 0.25 mg/ml had no effect on chromatid aberrations in human leukocyte cultures (no further details) (Tsuchiya & Hattori, 1976*).

In a mouse lymphoma assay (L5178Y cells), substantial increases in both "total mutant colonies" and "mutant frequency" values were observed at concentrations up to 3.7 mM DMP, with metabolic activation. However, the results were considered inconclusive by the authors who attributed the positive results to the presence of aldehyde metabolites (Barber et al., 2000).

In vivo

Brief summaries of in vivo cytogenetic assays were reported in the IUCLID for DMP (ECB, 2002). Equivocal results were noted for hepatocyte chromosome aberrations in the liver of rats from dermal applications of DMP at 1.25 g/kg bw/d for 1 month (Yurchenko, 1977*).

No increased frequencies were seen in bone marrow cell metaphases or chromatid exchanges in mice given an intraperitoneal injection of 1.4 g/kg DMP (Yurchenko, 1977*).

DMP was also reported to be negative in mouse (C57 B1) dominant lethal assays, with animals dosed by intraperitoneal injection (once only) or dermally 5 days/week for 2 months. For both tests the dose was 1250 mg/kg bw/d. No further details were available (Yurchenko, 1977*).

Data not reported in Previous Evaluations

Kubo et al. (2002) found DMP to be negative (with and without metabolic activation) in a modified Ames test in *S. typhimurium* strains TA98 and 100 at up to 100 nM DMP per plate.

Conclusion

Equivocal evidence exists for the mutagenic activity of DMP in *S. typhimurium.* Results appear dependent on the assay protocol, with TA100 and TA1535 being the only strains testing positive in some, but not all, assays. Metabolic activation inhibited these positive responses. Positive results were reported *in vitro* in hamster SCE but DMP tested negative in these cells for chromosomal aberrations. No effects were reported for chromatid aberrations

in human leukocyte cultures. DMP tested positive in mouse lymphoma assays with metabolic activation, however, the authors interpreted these results as possible false positives.

In vivo, equivocal results were noted for hepatocyte chromosome aberrations following dermal applications and negative results were noted for chromosome damage in bone marrow following intraperitoneal injections and in dominant lethal tests following intraperitoneal or dermal applications.

Overall, weight-of-evidence suggests that DMP is non-genotoxic.

3.7 Carcinogenicity

Previous Evaluations

No human data on carcinogenicity were available for DMP.

In an *in vitro* mammalian cell transformation assay, DMP was tested on Balb/c-3T3 mouse cells (Barber et al., 2000). With an exposure period of 72 hours and incubation over 4 weeks DMP did not induce statistically significant increases in transforming activity with concentrations up to 0.93µl/ml.

No *in vivo* carcinogenicity studies have been undertaken for DMP in laboratory animals. A 2-year chronic toxicity rat feed study (10 females/dose), with concentrations of DMP up to 4000 mg/kg bw/d did not report any neoplastic lesions, however details of the endpoints evaluated and organs studied were not available. No details of histological examinations were provided (Lehman, 1955).

In a one-year initiation/promotion study, DMP (3000 mg/kg bw/d) did not initiate (with the promoter 12-*O*-Tetradecanoylphorbol-13-acetate (TPA)) or promote (with the initiator 7,12-Dimethylbenz(a)anthracene (DMBA)) skin carcinogenesis in male Swiss CD-1 mice (50 per group). Mean body weights of mice treated with DMP were similar to vehicle controls throughout the study. A positive control response (squamous cell papillomas and carcinomas) was induced by DMBA and TPA in conjunction with acetone vehicle. In contrast, no animals treated with DMP with acetone or acetone vehicle alone showed any incidence of these neoplasms. The report concluded no evidence of tumour initiating or promoting activity of DMP (NTP, 1995).

Data not Reported in Previous Evaluations

No additional data were available.

Conclusion

Data are inadequate to determine the carcinogenic potential of DMP.

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, prenatal developmental 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 (as adults) and development (as foetuses) will then be discussed separately.

3.8.1 Human Studies

Previous Evaluations

Reduced fertility was reportedly seen in a group of women occupationally exposed to phthalates, including DMP (Aldyreva et al., 1975*). The study was considered inadequate on a number of aspects, including the lack of information on the selection of the unexposed control group and details of exposures to other substances and therefore no conclusions could be drawn.

Colon et al. (2000) found DMP (and other phthalates) in the serum of thelarche patients but not controls. However there was no statistically significant correlation between phthalate exposure and thelarche.

In vitro sperm cultures (from 'normal' men) were exposed to various concentrations of phthalates (including DMP), for up to 18 hours. Exposure to each of the phthalates including DMP resulted in a dose-dependent reduction in sperm velocity and straight-line motion (Fredricsson at al., 1993).

Data not reported in Previous Evaluations

Breast milk samples were analysed for 6 different phthalate monoesters in a Danish–Finnish cohort study on cryptorchidism, gonadotropins, sex-hormone binding globulin, testosterone and inhibin B. (Main et al., 2006). No association was found between MMP and cryptorchidism. MMP showed positive correlations with LH:free testosterone ratio. Association between 11 maternal urinary phthalate monoester concentrations and genital parameters such as anogenital distance and testicular descent in children was determined in 85 mother-son pairs (Swan et al., 2005). There was no significant association between maternal urinary MMP concentration and infant anogenital index (AGI) (anogenital distance divided by weight at examination).

Duty et al. (2003a; b) examined the levels of phthalate monoesters in urine of men attending an andrology clinic and also examined their semen quality and DNA damage in sperm. Eight urinary phthalate monoesters including monomethyl phthalate (MMP) were measured in a single spot urine sample collected on the same day as the semen sample. There was no dose-response relation between MMP and sperm or semen parameters, and urinary MMP levels were not associated with increased sperm DNA damage (as measured by comet assay).

Laboratory animal

3.8.2 Repeat dose toxicity studies

Previous Evaluations

Although no overt effects have been found in testes, DMP has been shown to significantly decrease testosterone levels in the serum and testes in rats after DMP was administered in diet at 2% (approximately 2000 mg/kg bw/d) to young male rats for 7 days (Oishi & Hiraga, 1980). The effect on reproductive performance was not studied.

3.8.3 Prenatal Developmental toxicity studies

Previous evaluations

Exposure of Sprague-Dawley dams (25-32 animals/dose), from gestational day (GD) 6-15, to concentrations of 0, 0.25, 1.0 and 5.0% DMP in feed (0, 200, 840 and 3570 mg/kg bw/d), resulted in reduced maternal food consumption with consequential loss of body weight gain in the high dose group. Relative liver weight was also increased in the high dose group. The NOAEL for maternal toxicity was determined at 840 mg/kg bw/d. No DMP-related effects (at any dose level) were observed on embryo/foetal development, including body weight and incidence of external, visceral and skeletal malformations (Field et al., 1993).

DMP (3500 mg/kg bw/d) administered by gavage to pregnant CD-1 mice (36 animals) from GD 7 - 15, did not elicit any signs of maternal toxicity or changes in body weight gain. No DMP-related effects were observed on foetal survival, litter size, litter weight or development (Plasterer et al., 1985).

Apart from a statistically significant reduction in body weight gain in the maternal high dose group, no evidence of maternal toxicity or developmental effects (gross, skeletal or visceral anomalies) was seen following dermal application of DMP at doses of 0, 0.5, 1.0 and 2.0 ml/d (applied by occluded dressing for 2 h/d) to Wistar rats (15-25 animals/dose) on GD 6-15 or GD 1-20 (Hansen & Meyer, 1989). There was no effect on numbers of implantations, corpora lutea or resorptions.

A developmental study was undertaken in Sprague-Dawley rats (5 females per dose) with 8 phthalate esters (including DMP) (Singh et al., 1972). DMP was administered by intraperitoneal injection on GD 5, 10 and 15 at doses of 0.338, 0.675 and 1.125 ml/kg bw (approximately 400, 800 and 1340 mg/kg bw). Untreated animals or animals treated with normal saline or cottonseed oil (at 5 and 10 ml/kg bw) comprised the control groups. Animals were killed and examined on GD 20. There was no effect on the number of corpora lutea. An increased number of resorptions was seen in both low and high dose but not intermediate dose. Numbers of dead foetuses increased in a dose-related trend with 9% foetal deaths at the highest dose. Foetal weights were significantly reduced (not dose related) in all dose groups. The frequencies of skeletal malformations were 25, 35 and 75% at low to high doses respectively, compared to 11% in controls. Malformations included missing tails/tail bones and/or eyes, elongated and fused ribs and incomplete skull bones. No details were provided regarding maternal toxicity.

Data not reported in Previous Evaluations

Sprague-Dawley outbred CD rats were treated by gavage daily from GD 12 to GD 19 at 500 mg/kg DMP per day. Limited data were presented, however, anogenital distance was not different to controls (Liu et al., 2005). Testes were isolated on GD 19 and DMP showed no significant effects on gene expression using a microarray analysis.

3.8.4 Developmental/Postnatal toxicity studies

Previous Evaluations

DMP administered by gavage to Sprague-Dawley dams (5 animals), at 750 mg/kg bw/d from GD 14 to postnatal day (PND) 3, did not elicit any effects on sexual differentiation in male offspring. Endpoints included testes weight, undescended testes, testicular testosterone production, anogenital distance, areola. Treatment did not induce overt maternal toxicity or have affects on litter size, pup weight or sex ratio (Gray et al., 2000).

Litter size and growth of pups up to PND 3 were unaffected by 3.5 or 5 g/kg bw/d gavage on GD 6-13 to mice despite 12/43 deaths among the dams in the high dose group (Hardin et al., 1987).

3.8.5 Mode of Action

DMP had no binding affinity for the oestrogen receptor and failed to prevent estradiol binding *in vitro* in rat (NCTR:SDN) uteri or human estrogen receptor α or ß (Nakai et al., 1999; Toda et al., 2004; Blair et al., 2000). DMP tested negative in a yeast two-hybrid assay as evaluated by its ability to induce hormone (β-galactosidase) activity, relative to 17β-estradiol induced activity (Nishihara et al., 2000). Similarly, DMP showed no oestrogenic activity *in vitro* in a recombinant yeast screen assay nor did it show any mitogenic activity in oestrogen responsive human breast cancer cells (MCF-7 assay) (Harris et al., 1997). At concentrations up to 400μM, the monoester metabolite, MMP (main metabolite of DMP) did not affect estradiol production in cultured rat ovarian granulosa cells (Lovekamp & Davies, 2001). MMP induced detachment of germ cells from a Sertoli cell monolayer *in vitro* but was 10,000 fold less potent than MEHP (Gray & Gangoli, 1986).

Conclusion

Effects on Fertility

The human and laboratory animal data are insufficient to assess adequately the effects of DMP on fertility. DMP significantly decreased testosterone levels in the serum and testes in young male rats following administration in diet at 2% (approximately 2000 mg/kg bw/d) for 7 days (Oishi & Hiraga, 1980). Reproductive performance in these animals was not assessed.

Developmental Effects

A single study (Singh et al., 1972) reports significant effects on development from intraperitoneal injection of DMP to rats. The foetuses were small, with an increased frequency of skeletal anomalies. No details of maternal effects were reported. All other studies (Plasterer et al., 1985; Hardin et al., 1987; Hansen & Meyer 1989; Field et al., 1993; Gray et al., 2000) have reported no effects for dosing by the oral or dermal route. The

NOAEL for developmental effects in a rat feeding study was 3570 mg/kg bw/d (highest dose tested). The disparity in results may be due to pharmacokinetic differences. Dosing by the intraperitoneal route will potentially expose the foetus to higher levels of the parent diester than oral ingestion where DMP is readily broken down to the monoester by esterases in the gastrointestinal tract and liver.

4. HAZARD CHARACTERISATION

DMP is absorbed via the gastrointestinal tract and via skin. Following absorption, DMP is distributed to multiple organs but rapidly cleared, with no accumulation. In rats over 7 days, approximately 6% per day of dermally applied DMP is absorbed and recovered in urine and faeces. *In vitro,* human epidermis is an order of magnitude less permeable to DMP than rat epidermis. Following oral administration in rats, the main DMP metabolites are the monoester (MMP) (78%) with free phthalic acid and unmetabolised DMP comprising the rest of the eliminated dose.

DMP is of low acute oral and dermal toxicity in rats, mice, rabbits and guinea pigs. Data are insufficient to determine the potential for inhalation toxicity.

DMP produces minimal skin irritant effects in animals and humans. It induces minimal eye irritation in rabbits. A single human case report noted eye irritation following contact with DMP. Available data from animals and humans suggests that DMP is not a skin sensitiser.

In repeat dose animal studies, the kidney appears to be the primary target organ, with effects on nervous system, lungs, liver and testes also reported. A NOAEL of 1000 mg/kg bw/d and a LOAEL of 2000 mg/kg bw/d based on reduced weight gains were determined in a 2-year feeding study in rats A repeat dose NOAEL of 1200 mg/kg bw/d and a LOAEL of 2400 mg/kg bw/d based on nephritis seen at this dose and above were determined from a 90-day dermal study in rabbits.

DMP showed equivocal evidence in both in vitro and in vivo genotoxicity studies. Equivocal evidence exists for the mutagenic activity of DMP in S. typhimurium strains TA 100 and TA 1535. However, these were the only strains testing positive. Positive results were reported *in vitro* in hamster SCE but DMP tested negative in these cells for chromosomal aberrations. No effects were reported for chromatid aberrations in human leukocyte cultures. DMP tested positive in mouse lymphoma assays with metabolic activation, however, the authors interpreted these results as possible false positives. *In vivo*, equivocal results were reported for hepatocyte chromosome aberrations and negative results were reported for chromosome damage in bone marrow and in dominant lethal tests. Overall, based on all data available and on a weight-of-evidence basis, DMP is unlikely to be genotoxic.

A 2-year rat feeding study did not report any neoplastic endpoints at concentrations of DMP up to 4000 mg/kg bw/d, however, details of endpoints evaluated and organs studied were not available. A one-year initiation/promotion study with dermal applications of 3000 mg/kg bw/d DMP in mice showed no evidence of carcinogenic initiation/promotion potential. A single mammalian cell transformation assay was negative. Overall, data are inadequate to determine the carcinogenic potential of DMP.

The human and laboratory animal data are insufficient to assess adequately the effects of DMP on fertility. A single study reported effects on development from intraperitoneal injection of DMP in rats. In contrast, other studies (oral and dermal) reported no effects. Data suggest that gestational exposure to DMP in rats or mice above doses likely to be maternally toxic have no developmental consequences. The NOAEL for developmental effects in a rat oral feeding study was 3570 mg/kg bw/d (highest dose tested).

5. HUMAN HEALTH HAZARD SUMMARY TABLE

Phthalate	***Acute Toxicity***	***Irritation & Sensitisation***	***Repeated Dose Toxicity***	***Genetic Toxicity***	***Carcinogenicity***	***Fertility***	***Developmental Toxicity***
Dimethyl (DMP)	Oral Rat: LD50 = 2860 – 10000 mg/kg bw Dermal Rat: LD50 = 38000 mg/kg bw	Skin Irritation: ME Eye Irritation: ME Sensitisation: negative	Oral Rat: NOAEL = 1000 mg/kg bw/d. LOAEL = 2000 mg/kg bw/d: ↓ body weight gain. Dermal Rat: NOAEL = 1200 mg/kg bw/d. LOAEL = 2400 mg/kg bw/d: nephritis High doses: nephritis, ↑ liver weight; ↓ liver cholesterol and total lipids; liver damage	*In vivo* Equivocal in chromosomal aberration tests Negative in SCE assay Negative in a dominant lethal assay *In vitro* Equivocal in bacterial mutation assays Positive in SCE assay Negative in chromosomal aberration tests Equivocal in a mouse lymphoma assay	*In vivo* Mouse: negative for initiation or promotion activity *In vitro* Negative in mammalian cell transformation assay.	Rat: Insufficient data	Developmental study Rat: NOAEL = 3570 mg/kg bw/d. LOAEL: NE (>3570 mg/kg bw/d) Maternal effects: Rat: NOAEL = 840 mg/kg bw/d LOAEL = 3570 mg/kg bw/d: ↑ liver weight; ↓ body weight gain

ME – minimal effects; NE – not established

6. REFERENCES

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7. ROBUST STUDY SUMMARIES

7.1. Reproductive Toxicity

Test substance	DEHP, BBP, DEP, DINP, DMP and DOTP
Species	Sprague-Dawley rats, age-90 days, Source-Charles River Breeding Laboratory, Raleigh, NC.
Route of admin.	Oral
Exposure period	GD 14 to PND 3
Study Duration	Onset of gestation to postnatal days 90-150
Frequency of treatm.	Daily
Doses	0, 0.75 g/kg bw/d
Control group	Corn oil vehicle
NOAEL maternal tox.	Nil
NOAEL teratogen.	Nil
Guidelines	Not mentioned
GLP	Not mentioned
Method	Pregnant dams were dosed orally with each of DEHP, BBP, DEP, DINP, DMP and DOTP at 0.75 g/kg bw/d in corn oil, from GD 14 to PND 3 (5-10 animals per group) Offspring body weight and anogenital distance (AGD) were recorded on PND 2 and one male pup/litter (randomly selected) was necropsied to measure testes weight. At PND 9-10, male pups were examined for haemorrhagic testes and at PND 13 for nipple retention. Male pups were weaned on PND 28 and divided into groups of 2-3. Offspring were necropsied at 3-5 months of age.
Result	No treatment-related maternal toxicity or reductions in litter size were seen. DEHP caused reduced maternal body weight gain (ca. 15g). DEHP and DINP significantly reduced pregnancy weight gain to GD 21, by 23% 14% respectively. DEHP and BBP caused significantly reduced live pup weight (ca. 15%). DMP, DEP and DOTP did not cause maternal toxicity or reduce litter size. DEHP and BBP caused reduced AGDs (ca. 30%) and reduced testes weights (ca. 35%) in male pups. DEHP, BBP and DINP caused significantly higher nipple retention (87%, 70% and 22%, respectively) and significant induction of reproductive malformations in males (82%, 84%, 7.7 respectively). DEHP and BBP caused testes retention and sex organ toxicity (agenesis of the bulbourethral glands, ventral prostate and seminal vesicles, and phallus clefting). DMP, DEP and DOTP did not appear to cause reproductive malformations or sex organ toxicity in male offspring.
Conclusion	BBP and DEHP significantly impaired sexual differentiation at 0.75 g/kg bw/d and also caused severe sex organ toxicity. DINP also impaired sexual differentiation to a lesser extent. DEP, DMP and DOTP were not developmental toxicants at this dose.
Reliability	

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