Human Health Hazard Assessment

Dimethyl terephthalate (DMT)
(CAS No. 120-61-6)

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INTRODUCTION

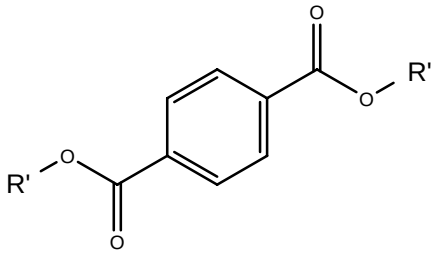
This review of dimethyl terephthalate (DMT) is a health hazard assessment only. For this assessment, an OECD SIDS Initial Assessment Report on Dimethyl Terephthalate (DMT) (OECD, 2001) was consulted. Information from this report was supplemented with relevant studies from more recent literature surveys 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:	120-61-6
Chemical Name:	1,4-Benzenedicarboxylic acid, dimethyl ester
Common Name:	Dimethyl terephthalate (DMT)
Molecular Formula:	$C_{10}H_{10}O_4$
Structural Formula:	
	R' = CH_3
Molecular Weight:	194.2
Synonyms:	Dimethyl 1,4-benzenedicarboxylate; Dimethyl p-benzenedicarboxylate; Dimethyl p-phthalate; Methyl 4-carbomethoxybenzoate; Methyl p-(methoxycarbonyl)benzoate; Terephthalic acid, dimethyl ester
Purity/Impurities/Additives:	Purity: 99.9% min. Impurity: 40 ppm max. methyl (p-formyl)benzoate; 225 ppm max. methyl hydrogen terephthalate Additives: none

1.2 Physicochemical Properties

Table 1: Summary of physicochemical properties

Property	***Value***

Physical state	White solid or colourless molten liquid
Melting point	141ºC
Boiling point	Not available
Density	Not available
Vapour pressure	$<1.33 \times 10^{-3}$ kPa (25°C)
Water solubility	0.019 g/L (25°C)
Partition coefficient n-octanol/water (log Kow)	2.25
Henry's law constant	Not available
Flash point	153ºC

Source: OECD (2001)

2. USES

DMT is used widely as an industrial intermediate to manufacture polyethylene terephthalate (PET) and dioctyl terephthalate (OECD, 2001).

In Australia, DMT is imported for distribution to various institutions and laboratories for analytical, pharmaceutical and biotechnological research.

3. HUMAN HEALTH HAZARD

3.1 Toxicokinetics

Previous Evaluations

Oral

Following a single or repeated oral dose to rats (20 or 40 mg/kg bw), ^{14}C-DMT was readily absorbed from the digestive tract. Excretion was almost complete within 48 hours, with 75-81% in urine and 4-16% in faeces. There was no evidence of tissue accumulation after multiple doses (Moffitt, 1975). In rats, terephthalic acid (TPA) was the only metabolite detected in the urine suggesting that the hydrolysis of DMT to TPA was virtually complete, while urinary metabolites in mice consisted of monomethyl terephthalate (70%) and TPA (30%) (Heck, 1980*).

Dermal

When ^{14}C-DMT was applied to unabraded depilated rat skin (80 mg in 0.2 mL vehicle) either as a single dose or on alternate days for 10 days under occlusion, around 11% of a single dose and 13% of five repeated doses were excreted in the urine and faeces of rats within 10 days (Moffitt, 1975).

Ocular

When ^{14}C-DMT was applied to rabbit eye, approximately 29% and 37% of the administered dose (50 mg) were excreted in the urine following 5 min or 24 h exposure with no evidence of tissue accumulation or ocular damage. Faecal excretion was minimal (≤2%) (Moffitt, 1975).

Data not Reported in Previous Evaluations

No data.

Conclusion

Several studies conducted in rats, rabbits, and mice have indicated that DMT is readily absorbed from the digestive tract and rapidly eliminated in the urine within 48 hours. Most of absorbed DMT is metabolised to TPA via hydrolysis. In mice, the predominant metabolite was monomethyl terephthalate. DMT is also absorbed dermally in rats.

3.2 Acute Toxicity

Previous Evaluations

The results for acute oral, dermal and inhalation toxicity in laboratory animals are summarised in the Table below.

Study	***Species***	***Results***	***References***
Oral	Rat	LD50 = 4390 mg/kg bw	Marhold, 1972*
		LD50 > 6590 mg/kg bw	Krasavage et al., 1973
Dermal	Guinea pig	LD50 > 5000 mg/kg bw	Patty's Ind Hyg Tox, 1981*
Inhalation	Rat	LC50 > 6 mg/L	Sanina & Kochetkova, 1963*

Data not Reported in Previous Evaluations

No data.

Conclusion

DMT has low acute oral, dermal and inhalation toxicity in laboratory animals.

3.3 Irritation

Skin Irritation

Previous Evaluations

Several unpublished studies were identified but lack details. DMT applied dermally to guinea pigs, mice (tails dipped into DMT solutions), and rabbits were reported to be slightly irritating (Eastman Kodak, 1957*, 1963*; Sanina & Kocketkova, 1963*).

Data not Reported in Previous Evaluations

No data.

Conclusion

DMT caused minimal skin irritation in laboratory animals.

Eye Irritation

Previous Evaluations

In two studies, DMT instilled in rabbit eyes had either no effect or induced a mild irritation (Eastman Kodak, 1957*; Anonymous, 1986*). A third study indicated that a pronounced

conjunctivitis was induced (time for return to normal was not reported) (Kamal'Dinova, 1962*).

Data not Reported in Previous Evaluations

No data.

Conclusion

DMT caused minimal eye irritation in rabbits.

Respiratory Irritation

Previous Evaluations

No data.

Data not Reported in Previous Evaluations

No data.

Conclusion

No respiratory irritation studies were available for assessment.

3.4 Sensitisation

Previous Evaluations

One study was available for assessing the skin sensitisation potential of DMT (Krasavage et al., 1973). In this study, 0.5 ml of a 1% solution of DMT in acetone:dioxane:guinea pig fat (7:2:1) was placed onto the rump area of 10 animals. Primary irritation was determined at 24 and 48 hours post-dosing. After one week, this dosing solution was mixed with whole heparinized rabbit blood (1%) for 1 to 3 hours and 0.05 ml of this mixture was injected into the footpad of the animals. A challenge dose (0.5 ml of a 1% solution of DMT in acetone:dioxane:guinea pig fat (7:2:1) was administered one week later. Sensitisation scores were recorded at 24 and 48-hours after the challenge dose. Neither primary irritation nor skin sensitization was induced by DMT.

Data not Reported in Previous Evaluations

No data.

Conclusion

DMT did not induce skin sensitisation in guinea pigs.

3.5 Repeated Dose Toxicity

Previous Evaluations

Several repeat dose toxicity studies have been conducted via oral (gavage and dietary) and inhalation routes of exposure. Studies range in duration from 2-13 weeks for the oral route and up to 6 months for the inhalation route.

Bladder stone induction was investigated in weanling F344 rats (13-18/sex/dose group) fed DMT diets for a period of two weeks at 0, 0.5, 1.0, 1.5, 2, or 3% (average dose for males/females was 660/638, 1320/1277, 1890/1790, 2260/2290 and 2590/3020 mg/kg bw/day). Bodyweights were decreased at 1.5% and above in females and at 1% and above in males on days 6-8 and 12-14. Decreased bodyweights were accompanied by reduced food consumption. The incidence of bladder calculi in males from the 0, 0.5, 1.0, 1.5, 2.0 and 3.0% groups were 0, 0, 0, 35, 72 and 100%, respectively, and in females 0, 0, 0, 0, 36, and 47%, respectively. Irregular thickening of the bladder wall was limited to animals having bladder calculi. The composition of the bladder calculi from the DMT treated animals was primarily calcium and TPA. The NOAEL was 0.5% (660 mg/kg bw/d for males) and 1.0% (1277 mg/kg bw/d for females) (Chin et al., 1981), based on bodyweight changes at higher doses.

Rats (7-19/group) were fed DMT via diet at 0.5, 1.6 or 3% for 13-weeks (Vogin, 1972*, cited in Heck & Tyl, 1985). The incidence of bladder calculi at 3% DMT was 12/16 and 6/16 in male and female rats, respectively. The incidence of bladder calculi in male rats was 1/19 at 1.6% and 2/19 at 0.5% DMT. Calculi were not noted in mid- and low-dose females. The incidence of mild to moderate hyperplasia of the bladder urothelium at 3% was 11/16 and 7/16 in males and females, respectively. Of the animals fed a 3% DMT diet and developing hyperplasia of the bladder lining, calculi were found in 11/11 males and 6/7 females. No NOAEL was determined.

Groups (10/sex/dose) of rats and mice were fed DMT in their diets at 1750, 2500, 5000, 10000, or 20000 ppm for 13-weeks (NCI, 1979*). No treatment-related effects were noted in physical appearance, behaviour or food consumption in either species. No deaths occurred in the rats. One male mouse at 2500, 5000, and 20000 ppm and two females at 20000 ppm died during the study. Reduced bodyweight gains were observed in both sexes of rats whereas body weight gains in mice were unaffected. No gross lesions were observed in either species at necropsy. Microscopic examination of the livers from both species in all dose groups revealed diffuse hepatocellular swelling but not in a dose-related manner. A NOAEL of 5000 ppm for rats and 20000 ppm for mice were derived.

DMT was evaluated in F344 rats and B6C3F1 mice (50/sex/dose) for carcinogenic potential in a 2-year dietary study (NCI, 1979*) (see Section 3.7). There were no effects on body weight or survival or clinical signs of toxicity reported from DMT in the diet at doses up to 0.5% (approximately 300 mg/kg bw/day), the highest dose tested.

Weanling male Long-Evans Hooded rats (30/group/dose) were exposed to DMT in the diet at 0, 0.25, 0.5 or 1% for 96 days (approximately 0, 152, 313 or 636 mg/kg bw/day) (Krasavage et al., 1973). Reduced weight gain was observed in the 1% dose animals. No effects were observed in haematological or biochemical parameters or absolute and relative liver and kidney weights. Microscope examinations were unremarkable. A NOAEL of 313 mg/kg bw/d was determined based on reduced weight gains at 636 mg/kg bw/day.

In a parallel study, male Long-Evans Hooded rats (30/dose) were exposed (whole body) to an atmosphere containing DMT at 0, 16.5, and 86.4 mg/m^3 for 4-hours per day for a total of 58 exposures over a 3-month period (Krasavage et al., 1973). The particulate respirable fraction

was 36%. Average daily doses were calculated at 0.7 and 4.0 mg/kg/day. Nose rubbing, preening and blinking were noted soon after the start of DMT exposures at the highest concentration. These symptoms continued intermittently throughout the exposure period and were repeated during succeeding exposures, but were not seen at the lower concentration. No toxicological effects were observed in biochemical or haematological parameters at any dose. Average and relative liver and kidney weights were unaffected. Tissue microscopic examination revealed no substance related changes. A NOAEC was assigned as 86.4 mg/m^3, the highest dose tested.

Rats and guinea pigs were exposed to DMT at 15 mg/m^3 for 6-hours per day, 5 days a week over a 6-month period (Lewis, 1982*). The respirable proportion was reported as 5 mg/m^3. There were no effects on body weights, clinical chemistry or urinanalysis parameters. Gross and histopathological evaluations were unremarkable. The NOAEC was 15 mg/m^3.

Rats exposed to 0.08, 0.4 or 1 mg/m^3 DMT by inhalation (described as a "chronic" exposure but duration not stated) induced a significant decrease (20% at 0.4 mg/m^3, 51% at 1 mg/m^3) in the uptake of radiolabelled noradrenaline by grey matter synaptosomes (Davidenko, 1984*). No effects were noted on monoamine oxidase or catecholamine-o-methyl transferase activity. No other details were provided.

Data not Reported in Previous Evaluations

No data.

Conclusion

Collectively, data suggest that the primary target organ for DMT is the urinary tract with metabolism of DMT to TPA and formation of bladder calculi. This effect is reported in some but not all studies. Liver effects (diffuse hepatocellular swelling) were also reported in a 13-week dietary study but not in any other studies.

In a 14-day dietary study in rats, a NOAEL was determined as 660 mg/kg/day (males) and 1277 mg/kg/day (females) based on decreased body weights at higher doses (Chin et al, 1981). In this study, a NOAEL for induction of urinary calculi was 1320 mg/kg/day (males) and 1790 mg/kg/day (females). In contrast, in a 96-day dietary study in rats, a NOAEL of 313 mg/kg/day was determined based on decreased body weight gains at 636 mg/kg bw/day. In this study, there was no evidence of urinary calculi.

Therefore, an overall conservative NOAEL for reduced body weight gains was determined at 313 mg/kg bw/day from a 96-day rat study.

Inhalation repeat dose studies report no toxicological effects, including no urinary effects. Only mild and transient nose rubbing, preening, and blinking were observed in a 3-month inhalation study. A NOAEC of 86.4 mg/m^3 was determined for inhalation exposure.

3.6 Genetic Toxicity

Previous Evaluations

The following genotoxicity studies were summarised from OECD (2001).

Test	***Test system (species/strain)***	***Dose***	***Metabolic activation***	***Result***	***Reference***
In Vitro					
Reverse mutation	*S. typhimurium* TA100, TA1535, TA98, TA1537	3.3-33 µg/plate	± S9	negative	Zeiger et al., 1982*
	S. typhimurium TA100, TA98	Unknown	± S9	negative	Kozumbo et al., 1982*
	S. typhimurium TA100, TA1535, TA98, TA1537, TA1538, TA102	0.5-5000 µg/plate	± S9	negative	Monarca et al., 1991*
	Photobacterium phosphorium	Unknown	± S9	negative	Elmore & Fitzgerald, 1990*
Unscheduled DNA synthesis	Rat hepatocytes	0, 727.5, 1455 or 2910 µg/mL	+ S9	negative	Monarca et al., 1991*
	SV40-transformed Chinese hamster cell line (CO60 cells)	0, 727.5, 1455 or 2910 µg/mL	- S9	negative	
	Human Hela cells	0, 5, 50 or 500 5000 µg/mL	± S9	negative	
	Hamster/Syrian (embryo cells)	0, 2.5, 5 or 10 µg/mL	- S9	negative	
Cytogenetic assay	Human lymphocytes	50-500 µg/mL	- S9	negative	Monarca et al., 1991*
Chromosomal aberration and sister chromatid exchange	Chinese hamster ovary cells (CHO)	10 µg/mL	± S9	negative	Loveday et al., 1990*
Mouse lymphoma mutation assay	L5178Y mouse lymphoma cells	0-100 µg/mL	± S9	negative	Myhr & Caspary, 1991*
In Vivo					
Sex-linked recessive lethality test	*Drosophila melanogaster*	1000 ppm (diet) or 400 ppm (injection) for 3 days	NA	negative	Foureman et al., 1994*
Micronucleus assay	B6C3F1 mice (bone marrow)	438-1750 mg/kg bw (intraperitoneal injection over 3 days)	NA	negative	Shelby*et al., 1993*
Micronucleus assay	(C57B1/6j x CBA)F1 mice (bone marrow)	0.20-1 mmol/kg bw (intraperitoneal injection)	NA	equivocal	Goncharova et al., 1988*

Data not reported in Previous Evaluations

No data.

Conclusion

The results from bacterial mutagenicity assays (Ames) all indicated that DMT is not mutagenic *(*Zeiger et al., 1982*; Kozumbo et al., 1982*; Monarca et al., 1991*; Elmore & Fitzgerald, 1990*). Negative results were also seen in *in vitro* DNA single-strand breakage assays, unscheduled DNA synthesis test, sister chromatid exchange assay, and in an assay evaluating the formation of micronuclei (Monarca et al., 1991*; Loveday et al., 1990*; Myhr & Caspary, 1991*). These studies utilised mouse hepatocytes, Chinese hamster embryo cells, HeLa cells, and human lymphocytes. Negative *in vivo* studies included a sex-linked recessive lethality test in Drosophila and one of two micronuclei studies in mice (Foureman et al., 1994*; Shelby et al., 1993*). The significance of an increase in micronuclei formation in one of these two *in vivo* tests is questionable due to many irregularities in the study's methodology as well as evidence of toxicity from the DMSO vehicle (Goncharova et al., 1988*). Furthermore, dose levels tested were much lower than those used in the other mouse micronuclei study (Shelby et al., 1993*) which showed a negative response.

On a weight-of-evidence basis, DMT is considered to be non-genotoxic.

3.7 Carcinogenicity

Previous Evaluations

DMT was evaluated for carcinogenic potential in a 2-year dietary study (NCI, 1979*). F344 rats and B6C3F1 mice (50/sex/dose) were administered DMT via diet at doses of 0, 0.25 or 0.5% (0, 2500, 5000 ppm). These exposure levels did not affect body weight, survival or induce any clinical signs of toxicity. A statistically significant increase in the incidence of pulmonary tumours was observed in male mice. However, this was not considered to be treatment-related because the incidence observed fell within the historical control range for male B6C3F1 mice. No increases in any other tumour types were noted in either species.

In another study of a DMT metabolite, Wistar rats were given TPA in the diet at 0, 1, 2 and 5% (0, 10000, 20000 or 50000 ppm) for 2 years (Gross, 1974*, cited in Heck & Tyl, 1985). Bladder calculi were seen in both sexes only at the highest dose (42/47 and 39/42 for males and females, respectively). Bladder and ureteral neoplasms occurred in 21/37 males and 21/34 females at 5%, in 1/48 male and 2/47 females at 2% and in 1/43 males at 1%. No urinary tract neoplasms were detected in low dose females or in controls. Pituitary and thyroid tumours were noted amongst both treatment and control groups. These were not related to TPA dose. The investigator concluded that the presence of stones causes changes in the epithelium of the urinary tract ranging from hyperplasia, papilloma, squamous metaplasia to transitional cell tumours and squamous cell carcinoma. No other details were provided.

Data not reported in Previous Evaluations

No data.

Conclusion

A 2-year carcinogenicity study of DMT showed no treatment-related carcinogenic effects. Available data indicate that DMT is not carcinogenic in rats and mice. A 2-year carcinogenicity study of a DMT metabolite, TPA, reported that high doses (up to 50000 ppm) were associated with bladder stone formation, urinary tract neoplasia and carcinoma.

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 repeat dose toxicity studies that dose adult animals for varying duration, one/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 Repeat dose toxicity studies

Data not reported in Previous Evaluations

To investigate the effects of TPA on testicular function, male Sprague-Dawley rats (5 weeks old, 10 animals/dose) were given TPA in diet at 0, 0.2, 1 and 5% for 90 days (Cui et al., 2004). Mean TPA intakes calculated from food consumption were 0, 189, 1177 and 5818 mg/kg bw/day, respectively. Testicular functions were assessed by histology, testicular sperm head counts, daily sperm production, sperm motility, biochemical indices (marker testicular enzymes), and serum testosterone. TPA did not cause testes weight loss (relative or absolute) but damage to spermatogenic cells and Sertoli cells at the 5% dose was observed. Decreased testicular sperm head counts, daily sperm production and sorbitol dehydrogenase activity were also seen at 5% TPA. Several characteristics of sperm motility such as VSL (straight line velocity), LIN (linearity), and STR (straightness) were reduced in all treated groups in a dose-dependent manner. Serum testosterone concentrations were not affected. There was no effect on food consumption or body weight of the rats.

3.8.2 One-generation reproductive toxicity studies

Previous Evaluations

Reproductive toxicity was evaluated in a one-generation reproduction study by exposing male Long Evans rats (30 rats/dose) to diets containing 0.25, 0.50 or 1.0% DMT for 115 days (Krasavage et al., 1973). These males were then mated with females that had been on the DMT diet for 6 days. After mating, females remained on the diet throughout pregnancy and lactation. No signs of toxicity were observed in either male or female parental animals. No effects on fertility parameters were noted. Pups born to parents fed 0.5 and 1.0% DMT had

significantly lower average body weights at weaning compared to the controls. This effect on the offspring was likely due to exposure to DMT through lactation and having access to the mother's food. The NOAEL was 1.0% (636 mg/kg bw/day – the highest dose tested) for systemic and fertility effects in parents and 0.25% (152 mg/kg bw/day) for their offspring.

In a one-generation reproduction study, no adverse effects on fertility were noted in adult CD or Wistar rats fed with 0, 0.03, 0.125, 0.5, 2 or 5% TPA (a major metabolite of DMT) in the diet for 90 days prior to mating, through the mating period and continuing through gestation and lactation (CIIT, 1982*). Slight strain differences were noted. Reduced bodyweight gains were observed in CD rats at 2% and 5% and Wistar rats at 5%. There was no effect in either strain on fertility and litter size. There were increased postnatal deaths on day 1 and decreased pup survivability to day 21 at 2% and 5% in Wistar rats and at 5% for CD rats. Several litters of Wistar pups were lost to dams suffering obvious signs of maternal toxicity. Unscheduled deaths occurred during the post-weaning period in the 5% groups and was associated with a very high incidence of renal and bladder calculi in both rat strains. Weanling animals exhibited a higher incidence of calculi compared to adults consuming the same dietary level of TPA. The NOAEL for maternal and developmental toxicity was 0.5% (240-307 mg/kg bw/day), while the NOAEL for fertility effects was >5.0% (2480-3018 mg/kg bw/day).

3.8.3 Prenatal developmental toxicity studies

Previous Evaluations

Exposure to 1000 mg/kg bw/day DMT via gavage from GD 7-16 in Wistar rats (sacrificed on day 21) had no effect on development (Hoechst, 1986*). Inhalation exposure in thirty rats to DMT at 1 mg/m^3 throughout gestation had no effect on development (Krotov & Chebotar, 1972*). No further details were available for these studies.

Inhalation exposures to TPA at levels of 1, 5, and 10 mg/m^3 (6 hours/day) from GD 6-15 in Sprague-Dawley rats had no effect on litter weights, pup viability or number of fetal malformations (Amoco Corporation, 1989*; Ryan et al., 1990*). A slight increase in rib anomalies was noted in the middle dose group, but rib anomalies were not considered to be an indicator of teratogenesis because they were common variations, not elevated in a dose-related manner, and within the range of historical controls.

Conclusion

Fertility effects

DMT in the diet up to 1% (636 mg/kg bw/day) had no effect on reproduction (Krasavage et al., 1973).

In a one-generation reproduction feeding study on TPA, no adverse effects on fertility were noted in adult rats fed up to 5% TPA (CIIT, 1982*). The NOAEL for fertility effects was >5.0% (2480-3018 mg/kg bw/day). Results of a recent study (Cui et al., 2004) on TPA showed that sperm head counts and daily sperm production decreased significantly in the 5% (5818 mg/kg bw/day). In addition, several sperm motility parameters were also reduced significantly in all treated groups.

Developmental Toxicity

DMT in the diet was associated with decreased pup weight at weaning but this effect was likely due to direct exposure to DMT through lactation and having access to the mother's food (Krasavage et al., 1973). The NOAEL for developmental effects was 152 mg/kg bw/day and the LOAEL 313 mg/kg bw/day, based on decreased body weight at weaning. The NOAEC in a developmental study for DMT was 1 mg/m^3.

The NOAEL for oral exposure to TPA was at 0.5% (240-307 mg/kg bw/day) based on increased postnatal deaths and decreased pup survivability at higher doses (CIIT, 1982*). The NOAEC in a developmental study for TPA was 10 mg/m^3.

4. HAZARD CHARACTERISATION

Toxicity data for DMT were available for the majority of health endpoints. Additional data from terephthalic acid (TPA) are presented as TPA is a major metabolite of DMT.

DMT was readily absorbed after oral administration. Elimination was rapid with urine being the major route of excretion. There was no evidence of accumulation in tissues after multiple doses. The hydrolysis product, TPA, was the only metabolite detected in the urine in rats, while urinary metabolites in mice consisted of monomethyl terephthalate (70%) and TPA (30%).

DMT has low acute oral, dermal and inhalational toxicity. The acute oral LD50 value in rats is 4390 – >6590 mg/kg bw, the dermal LD50 in guinea pigs is >5000 mg/kg bw, and the inhalational LC50 in rats is >6 mg/L.

DMT causes minimal skin and eye irritant effects in animals, and did not induce skin sensitisation in guinea pigs.

DMT does not appear to be mutagenic or genotoxic, nor was it deemed to be carcinogenic based on a 2-year feeding study.

For repeat dose toxicity, a conservative NOAEL based on reduced body weight gains in a rat 96-day dietary study was determined at 313 mg/kg bw/day. The target organ identified in oral exposure studies was the urinary tract with effects attributable to metabolism of DMT to TPA and the subsequent formation of bladder crystals or calculi primarily composed of Ca-TPA. In rats, bladder calculi formation occurred at a minimum DMT exposure length of 14 days at a dietary concentration of 1.5% (1890 mg/kg bw/day) for male rats and 2% (2290 mg/kg bw/day) for female rats.

Following 90-days of exposure via the inhalation route, a NOAEL of 86.4 mg/m^3 was determined. Clinical effects at this dose, such as nose rubbing, preening, and blinking, were considered mild and transient. No urinary effects were observed following inhalation exposure.

In a one-generation reproduction study, DMT in the diet up to 1% (636 mg/kg/day) had no effect on reproduction although pup weights were reduced at weaning (Krasavage et al., 1973). There was no evidence of fertility toxicity, and hence the NOAEL for fertility was 636 mg/kg/day, the highest dose tested. In the same study, the NOAEL for developmental effects was 152 mg/kg/day, with a LOAEL of 313 mg/kg/day based on reduced pup weights at weaning, which were probably a lactational effect. The NOAEC in an inhalation developmental study for DMT was 1 mg/m^3 and NOAEL in an oral developmental study was 1000 mg/kg.

The DMT metabolite, TPA, was also examined in reproduction studies. In a one-generation reproduction feeding study, no adverse effects on fertility were noted in adult rats fed up to 5% TPA (2480-3018 mg/kg bw/day). While the NOAEL for fertility effects was >5.0% (2480-3018 mg/kg bw/day), the NOAEL for maternal toxicity was 0.5%. The NOAEL for developmental toxicity was 0.5% (240-307 mg/kg bw/day), based on increased postnatal deaths and decreased pup survivability at higher doses. The adverse effects observed in the

offspring in this study appear to be the result of maternal toxicity and the formation of renal and bladder calculi in the weanling animals. Results of a recent study showed that sperm head counts and daily sperm production decreased significantly in rats fed 5% TPA in the diet (5818 mg/kg bw/day). In addition, several sperm motility parameters also reduced significantly in all treated groups. In a development study, the NOAEC for TPA was 10 mg/m^3.

Overall, DMT and its metabolite TPA do not appear to affect fertility. However, at high doses (5% in the diet), TPA has been shown to damage spermatogenic and Sertoli cells and reduce spermatozoa motility. No developmental effects were observed with DMT in inhalation and oral studies. TPA caused developmental effects at maternally toxic doses.

5. HUMAN HEALTH HAZARD SUMMARY TABLE

Phthalate	***Acute Toxicity***	***Irritation & Sensitisation***	***Repeated Dose Toxicity***	***Genetic Toxicity***	***Carcinogenicity***	***Fertility***	***Developmental Toxicity***
Dimethyl terephthalate (DMT)	Oral Rat: LD50 = 4390 – > 6590 mg/kg bw Dermal Guinea pig: LD50 > 5000 mg/kg bw Inhalation Rat: LC50 >6 mg/L	Skin irritation: Minimal effects Eye irritation: Minimal effects Respiratory irritation: No data Skin sensitisation: Negative	Rat: Oral NOAEL = 313 mg/kg bw/d LOAEL = 636 mg/kg bw/d, ↓ body weight gains. Inhalation NOAEL = 1 mg/m^3 High doses: Bladder calculi and urothelial hyperplasia.	*In vitro* Negative in Ames test, DNA damage, sister chromatid exchange and micronuclei assays *In vivo* Negative in sex-linked recessive lethality and micronuclei tests	Rat, mouse: no treatment-related carcinogenicity. NOAEL = 300 mg/kg bw/d	Rat: NOAEL = 636 mg/kg bw/day LOAEL = not established	One-generation study Rat: NOAEL = 152 mg/kg bw/day LOAEL = 313 mg/kg bw/day, ↓ pup weight at weaning Gestational study Rat: NOAEL = 1000 mg/kg bw/d LOAEL = not established

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