FOREWORD INTRODUCTION

Dimethyl terephthalate

CAS N°: 120-61-6

SIDS Initial Assessment Report

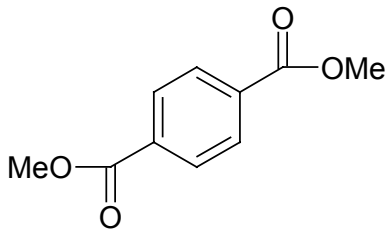
For

SIAM 11

United States, January 23-26, 2001

1. Chemical Name:	Dimethyl terephthalate
2. CAS Number:	120-61-6
3. Sponsor Country:	United States/IT
	National SIDS Contact Point in Sponsor Country: Oscar Hernandez Director, Risk Assessment Division Office of Pollution Prevention and Toxics US EPA Washington, DC 20460
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	
• Process used	
6. Sponsorship History	SIAM 3—Removed from Agenda for further work.
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	
7. Review Process Prior to the SIAM:	
8. Quality check process:	
9. Date of Submission:	November 7, 2000
10. Date of last Update:	
11. Comments:	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	120-61-6
Chemical Name	Dimethyl Terephthalate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

Data for dimethylterephthalate (DMT) is available for all SIDS health endpoints. However, for reproductive and developmental toxicity, the available data on DMT is not considered sufficient to support a conclusion that these endpoints have been completed. As a result, additional data from terephthalic acid (TPA) is being presented to support the conclusion that the reproductive and developmental toxicity endpoints have been completed. The use of TPA data for health endpoints is acceptable due to the principle that DMT metabolizes to form TPA.

Human Health

Results from acute toxicity studies via the oral, dermal and inhalation routes indicate that DMT is of a low order of toxicity. Oral acute toxicity studies in rats reported LD50s of 4,390 to >6,590 mg/kg. Inhalation and dermal LC and LD50s in rats and guinea pigs were >6 mg/L and >5,000 mg/kg, respectively. In several animal studies, DMT is indicated to be slightly irritating to both the skin and eyes. Available data indicate that DMT is not considered to be sensitizing in guinea pigs.

Numerous repeat dose studies have been conducted via oral (gavage and dietary) and inhalation routes of exposure. Studies range in duration from 2-13 weeks via the oral route and up to six months for inhalation administrations. Collectively, the data indicate that the primary target organ is the urinary tract due to DMTs metabolism to TPA and the formation of renal crystals or calculi and their sequelae on the soft tissues. In a 14-day feeding study in rats a NOEL based on decreased body weights was seen in males at 660 mg/kg/day (0.5% in diet) and in females exposed to 1277 mg/kg/day (1.0% in diet) (Chin et al, 1981). In the same study, a NOEL for induction of urinary calculi was 1320 mg/kg (males) and 1790 mg/kg females (1.5% in diet). In a 96-day feeding study in rats, a NOEL, based on decreased body weight gains, of 313 mg/kg/day (0.5% in diet) and a LOAEL of 636 mg/kg/day (1% in diet) was determined. However, in this study, there was no evidence of urinary calculi (Krasavage et al., 1973). Thus, the formation of urinary calculi and its secondary effect on soft tissues occurred at a minimum DMT exposure length of 14 days at a dietary concentration of 1.5% for males (1,890 mg/kg) and 2% in females (2,290 mg/kg). Based on urinary solubility of Ca-TPA, normal human urine would become saturated with Ca-TPA at a TPA concentration of approximately 8-16mM. Assuming an average volume of urine excreted by humans is 1.5 L/day and that DMT is metabolized entirely to TPA, then the amount of DMT that would have to be absorbed to produce 8mM minimum saturating concentration of TPA is 2,400 mg/kg/day. Inhalation repeat dose studies do not show the primary urinary effect observed in the oral studies, however, following 90-days of exposure via the inhalation route, a NOAEL of 16.5 mg/m^3 was determined for the following effects: mild and transient clinical effects-nose rubbing, preening, and blinking. In the same study, a LOAEC of 86.4 mg/m^3 was established.

Given the weight of evidence, DMT does not appear to be mutagenic or genotoxic in numerous *in vitro* (bacterial and mammalian systems) and several *in vivo* studies. In addition, DMT was not deemed to have carcinogenic effects in a two year feeding study in male and female rats and female mice, but equivocal evidence was noted in male mice.

In developmental toxicity studies, two on DMT and one on TPA, there is no evidence of developmental toxicity. In inhalation studies, the NOAEC for DMT was 1 mg/m^3 and for TPA it was 10 mg/m^3 (both were the highest dose tested). In a gavage study on DMT, a NOAEL of >1000 mg/kg was determined. In a 115-day oral feeding study to assess the reproductive toxicity potential of DMT, a NOEL of 636 mg/kg/day (1.0% in diet; highest dose tested) was determined for parental effects while the NOEL for offspring was 152 mg/kg/day based on reduced pup weights at weaning. This effect was likely due to exposure to DMT through lactation and having access to the mother's food and hence it is a primary toxicity of DMT. Since this study's methodology varies from the current OECD guidelines, data from the DMT metabolite TPA is used to support this endpoint. In a one-generation reproduction feeding study on TPA, postnatal growth weight and mortality effects were observed in pups. The NOAEL for maternal toxicity and for the F1 offspring was 0.5% (240 to 307 mg/kg), while the NOAEL for reproductive effects was >5.0% (2480-3018 mg/kg) TPA in the diet. 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 found in the weanling animals.

Environment

The physical-chemical properties of DMT include a melting point of 141^{0}C, a vapor pressure of 0.01 mmHg at 25^o C, a water solubility of approximately 19 - 37mg/l, a partition coefficient of log Kow 2.25 and a flash point of 153 ^{0}C. Overall, DMT undergoes slow abiotic hydrolysis (half-life 321 days), has a photo-oxidation half-life of weeks, and stability in surface and ground water with half-lives of weeks. However, the potential for significant environmental releases are low and the material is classified as readily biodegradable (84%, MITI test).
This chemical is moderately toxic to fish (96h LC50 = 9.6 mg/L), daphnids (48h LC50 = 30.4 mg/L), and green algae (72h EC_{50} biomass = 27.6 mg/L; 72h EC_{50} growth rate >32.3 mg/L). However, it is not expected to bioaccumulate in fish and is not expected to biomagnify via food chains. Using an assessment factor of 100 and the fish toxicity value, a PNEC of 0.096 mg/L is derived.

Exposure

Dimethyl terephthalate is produced (2004 world nameplate capacity estimate 4,936,000 tonnes or 1.09E10 pounds) in closed systems and used primarily within its own manufacturing facilities as a building block in the synthesis of polyethylene terephthalate plastics. It is also used as an intermediate to manufacture dioctyl terephthalate. When transported, it is shipped in bulk containers. Human exposures are in general very minimal and limited. The main occupational exposure concern in processing is that of direct physical burns due to accidental dermal contact to DMT in its molten state. Consumer exposure is possible via residual levels of less than 1 ppm DMT in PET-polymers.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

No recommendation for further work.

FULL SIDS SUMMARY

STUDY (CAS NO 120-61-6)		SPECIES	PROTOCOL	RESULTS
PHYSICAL CHEMISTRY				
2.1	Melting Point or Decomposition Point			141° C
2.2	Boiling Point			280° C and 288° C
2.3	Vapor Pressure			100 mmHg at 208° C; 1.15 mmHg at 93° C; 0.01 mmHg at 25° C
2.4	Partition Coefficient (Log Pow)			2.25
2.5	Water Solubility			19 mg/L (20°C) 37.2 mg/L (25° C)
2.6	Flashpoint		Cleveland, open cup	153° C
2.7	Flammability			NA
2.8	pH in water			NA
2.9	Other data: Explosive limits (Lower) Viscosity Surface Tension			 0.000033 mg/L NA NA
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Biodegradability		Chemical oxygen demand (aerobic)	COD = 1.70 g oxygen
			Japanese MITI test	Theoretical BOD = 84%
			River water and sea water tests	100% degradation in river water and up to 49% in sea water.
		Pseudomonas acidovorans	Incubation test	No degradation was noted.
		Rhodococcus	Incubation test	100% degradation
		Rhodococcus	Soil and wastewater inoculation tests	100 % degradation
		Bacillus sp.	Incubation test	DMT was its sole carbon source.
		Aspergillus niger	Incubation test	58% degradation after 144 hours
3.1.2	Sewage Treatment		Secondary waste water	IC_{50} = >5000 mg/L
3.1.3	Stability in air		Hydroxyl radical and ozone reactivity	$t_{1/2} \cong$ 3 days unreactive toward ozone.
			Photooxidation half-life	$t_{1/2}$ = 4.7 – 46.6 days.
	Stability in water		Alkoxyradical reactivity	Unreactive
			Hydrolytic half-life	321 days
			Half-life	Surface water $t_{1/2}$ = 1-4 Groundwater $t_{1/2}$ = 2-8 weeks
			Octanol water partition coefficient	LogP = 2.25
			Log sediment organic content/water partition coefficient	K_{oc} = 2.49
	Stability in soil		Half-life	1-4 weeks.
3.1.4	Identification of main mode of degradability in actual use	No specific studies available		
3.2	Bioaccumulation		Bioconcentration factor (Log)	BCF = 1.21
3.3	Photodegradation		Photooxidation half-life	4.7 – 46.6 days.

ECOTOXICOLOGICAL DATA				
4.1	Toxicity to fish			
4.1.1	Acute test	Fathead minnow	96 hr, static	LC_{50} = 9.6 mg/L
		Fathead minnow	96 hr, static	LC_{50} = 45 mg/L
		Fathead minnow	96 hr	LC_{50} = 14.2 mg/L
4.1.2	Results of long-term tests (e.g. prolonged toxicity) early life state	No studies available		
4.2	Toxicity to Daphnids			
4.2.1	Acute tests	*Daphnia*	96 hr	LC_{50} = >100 mg/L
		Daphnia	48 hr	EC_{50} = >30 mg/L
		Daphnia	48 hr	LC_{50} = 30.4 mg/L
4.2.2	Results of longer-term tests (e.g. reproduction)	No studies available		
4.3	Toxicity to algae	*Scenedesmus* *Subspicatus*	72 hr	Biomass EC_{50}: 27.6 mg/L EC_{10}: 14.3 mg/L NOEC: 10.8 mg/L Growth Rate EC_{50}: >32.3 mg/L EC_{10}: 20.1 mg/L NOEC: 10.8 mg/L
4.4	Toxicity to other aquatic organisms	Flatworm	96 hr, static	LC_{50} = >100 mg/L
		Snail	96 hr, static	LC_{50} = >30 mg/L
		Snail	96 hr, static	LC_{50} = >100 mg/L
		Sideswimmer	96 hr, static	LC_{50} = >30 mg/L
4.5	Toxicity to Bacteria	No studies available		
4.6	Toxicity to terrestrial organisms	No studies available		
4.6.1	Toxicity to Soil-dwelling organisms	No studies available		
4.6.2	Toxicity to Plants		Germination Effects	NOAEC = 10 mg/L (Rye grass) NOAEC = 30 mg/L (Radish, Lettuce)
				NOAEC = 10 mg/L (Rye grass, Radish) NOAEC = 1 mg/L (Lettuce)
			Seedling Effects	33 mg/L (Corn) 33 mg/L (Marigold) 33 mg/L (Lettuce) 10 mg/L (Radish)
				1000 mg/L (Radish, Marigold, Lettuce) 100 mg/L (Corn)
4.6.3	Toxicity to insects	No studies available		
4.6.4	Toxicity to Birds	No studies available		
4.7	Biological effects monitoring (including biomagnification)		Bioconcentration factor (Log)	BCF = 1.21
4.8	Biotransformation and Kinetics in Environmental Species	No studies available		
TOXICOLOGICAL DATA				
5.1	Acute Toxicity			
5.1.1	Acute Oral	Rat	20% solution in corn oil	LD_{50} > 6,590 mg/Kg
		Rat		LD_{50} = 4,390 mg/Kg
5.1.2	Acute Inhalation	Rat	Aerosol	LC_{50} = >6 mg/L
5.1.3	Acute Dermal	Guinea Pig	Unknown	LD_{50} = >5,000 mg/Kg
5.1.4	Acute other route	No studies available		
5.2	Corrosive/irritation	Guinea Pig	Inhalation via gauze	Slight redness, no edema
		Guinea Pig	Inhalation via gauze	Erythema and slight to moderate edema
		Mouse	Dermal, tails	A transient slight and behavioral changes
		Rabbit	Dermal, shaved skin	A slight irritation and pigmentation
5.3	Skin sensitization	Guinea Pig	Dermal, rump and	No sensitization response

			shoulders	
		Guinea Pig	Dermal, rump and footpads	No sensitization response
		Guinea Pig	Dermal	Slight irritation, no sensitization response
5.4	Repeat Dose	Rat	10 days, oral gavage	No NOEL was determined.
		Rat	14 days, oral diet	NOEL = 0.5% (male rats) NOEL = 1.0% (female rats)
		Rat	16 days, oral diet	A NOEL was not determined.
		Rat	28 day, oral diet	No hematological or histopathological abnormalities.
		Rat	>34 days, oral	NOEL = 500 mg/kg.
		Rat	13 weeks, oral	A NOEL was not determined.
		Rat and Mouse	13 weeks, oral diet	NOAEL = 5000 ppm (rats) NOAEL = 20000 ppm (mice)
		Rat	96 days, oral diet	NOEL = 313 mg/kg
		Rat	5 months, inhalation	30% mortality, rhinitis, depilation, dystrophic changes in the liver and kidneys, hemorrhage of the lungs, brain and myocardium, and hyperemia of the internal organs
		Rat	3 months, inhalation	NOEL = 16.5 mg/m^3 .
		Rat and Guinea Pig	6 months, inhalation	NOEL = 15 mg/m^3.
		Rat	Chronic, inhalation	A NOEL was not determined.
		Rat	Chronic inhalation	A NOEL was not determined.
		Rat	2.5 months, subcutaneous	reduced body weight gain.
5.5	Genetic Toxicity			
5.5.1	Bacterial Test	*Salmonella typhimurium* (strains TA1535, TA1537, TA98, TA100)	Ames assay	Negative +/- metabolic activation
		Salmonella typhimurium (strains TA98 and TA100)	Ames assay with modifications	Negative +/- metabolic activation
		Salmonella typhimurium (strains TA1535, TA1537, TA98, TA100, TA102, TA1538)	Ames assay	Negative +/- metabolic activation
		Photobacterium phosphorium	Mutatox™ Assay	Results were considered equivocal.
5.5.2	Non-bacterial in vitro Test	Rat hepatocytes and Chinese hamster embryo cells	DNA single-strand break assay	Negative
		HeLa Cells	Unscheduled DNA synthesis assay	Negative
		Human Lymphocytes	Chromosomal aberration assay	Negative
		Human Lymphocytes	Micronuclei assay	Negative
		Syrian Hamster Embryo	DNA amplification assay	Negative
		Mouse Lymphoma	Gene mutation assay	Negative
		Chinese Hamster Ovary	Chromosomal aberration assay	Negative
		BALB/c-3T3 Cells	Transformation assay	Indeterminate activity

5.5.3	Non-bacterial in vivo test	*Drosophila melanogaster*/ Canton-*S* males and *Basc* females.	Sex-linked reessive lethal assay	Negative
		Mouse	Micronuclei assay	Negative
		Mouse	Micronuclei assay	Positive
		Drosophila melanogaster	Sex-linked dominant lethal assay	Positive
5.6	Carcinogenicity	Rat and Mouse	2 year, oral diet	Negative in rats or female mice. An increase in lung tumors in male mice was considered equivocal.
5.7	Reproductive and Developmental toxicity	Rat	115 days, oral diet	NOEL =636 mg/kg (P1) NOEL = 152 mg/kg (F1)
		Rat	> 150 days, oral diet Parental effects: CD(M) CD(F) Wistar(M) Wistar(F) Reproductive: CD(M) CD(F) Wistar(M) Wistar(F) Offspring effects: CD(M) CD(F) Wistar(M) Wistar(F)	 NOAEL = 240 mg/kg NOAEL = 282 mg/kg NOAEL = 960 mg/kg NOAEL = 1219 mg/kg NOAEL > 2499 mg/kg NOAEL > 2783 mg/kg NOAEL > 2480 mg/kg NOAEL > .3018 mg/kg NOAEL = 240 mg/kg NOAEL = 282 mg/kg NOAEL = 960 mg/kg NOAEL = 1219 mg/kg
5.7.1	Reproductive toxicity: single generation reproductive toxicity study with teratology screen	No studies available		
5.7.2	Teratogenicity/Developmental Toxicity	Rat	Gestation, inhalation	No abnormalities were reported.
		Rat	7-16 day gestation, oral gavage	NOAEL >1,000 mg/kg.
		Rat	6-15 day gestation, inhalation	NOAEL >10 mg/m^3 TPA.
6.	Neurotoxicity	No studies available		
7.	Experience with Human Exposure	Human	Dermal	No irritant effects
		Human	Not reported	A Russian study reported no effects in workers exposed to high concentrations.
		Human	Not reported	A Russian study reported a moderate leukocytosis in workers involved in DMT synthesis.
7.1	Biological Monitoring	No studies available		
	Toxicodynamics and Toxicokinetics	Rat	5 day, oral diet	DMT is readily absorbed and primarily excreted by the kidney as terephthalic acid.
		Rat and Rabbit	The fate of a radiolabeled DMT was followed using ocular, dermal, oral, and intratracheal exposure routes.	DMT was not well absorbed by dermal, ocular, or even intratracheal exposures compared to oral. In all cases DMT was rapidly eliminated and primarily in urine.
		Rat and Mouse	Animals received a single oral dose of radiolabeled DMT. Feces and urine were collected over a 48-hour period.	90% was recovered in the urine and less than 1% was present in carcasses. In rats it was all terephthalic acid (TPA). In mice 70% was monomethyl terephthalate and

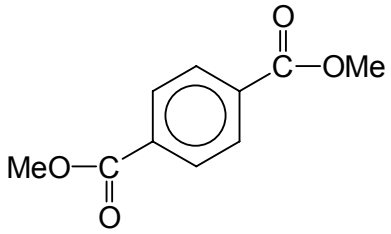
				30% was TPA.
		Rat	Animals were fed diets with 0, 1.0 or 2.0% DMT for 3 weeks.	Animals developed hypercalciuria and had urinary acidosis. DMT was metabolized to TPA.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 120-61-6
IUPAC Name: Dimethyl terephthalate
Molecular Formula: C10H10O4
Structural Formula:



Molecular Weight: 194.19
Synonyms: dimethyl 1,4-benzenedicarboxylate
dimethyl p-benzenedicarboxylate
dimethyl p-phthalate
methyl 4-carbomethoxybenzoate
methyl p-(methoxycarbonyl)benzoate
terephthalic acid, dimethyl ester

Physical description: white solid, or colorless molten Liquid

1.2 Purity/Impurities/Additives

Degree of purity: 99.9% minimum

Major impurities: Methyl (p-formyl)benzoate – 40 ppm max.

Methyl hydrogen terephthalate – 225 ppm max.

Essential additives: None

1.3 Physico-Chemical properties

Water solubility: 19 mg/L (25^{o} C);

Partition coefficient: logP = 2.25; P = 178

Vapor pressure: 0.01 mm Hg 25°C

Melting point: 141^{o} C (286^{o} F)

Flash point: 153^{o} C (308^{o} F)

Biodegradation: Readily biodegradable

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Production Volume

Total annual North American nameplate (maximum capacity) production capacity is estimated for 2004 at 1,917,000 mt or 4.23E9 pounds (SRI Consulting Jan. 2000).

Total annual worldwide nameplate production capacity is estimated for 2004 at 4,936,000 mt or 1.09E10 pounds (SRI Consulting Jan. 2000).

Manufacturing Process

In the United States, dimethyl terephthalate (DMT) is manufactured by the air oxidation of p-xylene in an enclosed continuous process. It is purified by distillation and transferred through closed lines and stored in tanks as a molten liquid.

Use

Dimethyl terephthalate is used as an industrial intermediate to manufacture polyethylene terephthalate (PET) and dioctyl terephthalate. A good proportion of these end-uses occur at the same plant site as its initial synthesis. Some DMT is sold to other producers, also for the manufacture of polyethylene terephthalate. Transfer to other plant sites is as the molten liquid in tank cars or trucks.

Form of marketed product

Molten liquid

2.2 Environmental Exposure and Fate

2.2.1 Releases and Sources

The primary source of release is permitted stack air emissions and possible fugitive air emissions. These emissions, while not measured, are believed to be low as a result of the limited volatility of DMT. Emissions to waterways, which also are not measured, are also believed to be negligible. In the U. S., DMT is not listed as a Toxic Release Inventory (TRI) chemical under EPCRA 313, or as a Hazardous Air Pollutant. Aqueous waste streams from the manufacturing and use processes are sent to on-site corporate waste-water treatment facilities for biooxidation prior to release into public waterways. Because DMT has limited water solubility and is readily biodegradable, any DMT released from the on-site waste-water treatment systems to waterways is believed to be negligible. Organic waste streams from the manufacturing and use processes are incinerated.

Fugitive Emissions

Although fugitive emissions have not been determined, such emissions are expected to be low. Manufacture, use and storage as an industrial intermediate take place within closed continuous equipment and DMT has very limited volatility.

2.2.2 Environmental Fate

Dimethyl terephthalate is a solid with limited vapor pressure (100 mmHg at 208^{o} C; 0.01 mmHg at 25^{o} C; 1.15 mmHg at 93^{o} C) and low water solubility (28.7 mg/L (20^{o} C); 19 mg/L (25^{o} C); 37.2

mg/L (25^{o} C). When DMT was placed in wastewater it was readily degraded by microbes (BOD reduced up to 95% in 48-hours), and when mixed with sludge, it had a theoretical BOD of 84% (MITI, 1992). When DMT was placed in secondary wastewater, an IC_{50} was determined to be >5000 mg/L (DMT was in a suspension). Because DMT biodegrades readily, it is expected to partition primarily to water and soil, where it will biodegrade and not persist or bioaccumulate (logP = 2.25). Bioconcentration and absorption to sediment are also not expected to be very important fate processes in aquatic environments (log BCF = 1.21 and Koc = 2.49). Dimethyl terephthalate has a photooxidation half-life of 4.7 to 46.6-days (Howard, *et al*.)

If released into water, DMT is expected to degrade by simple hydrolytic processes with half lives of 321-days at neutral pH (Mabey and Mill, 1978). It has an estimated half-life of 1-4 weeks for surface water and 2-8 weeks for ground water (Howard, *et al*.). In studies with river water, 50 ppm of DMT were degraded in 3-days (Kondo, *et al*., 1988).

If released into air, vapor phase DMT will react with photochemically-produced hydroxyl radicals and have an estimated half-life of approximately 5 to 47-days (Howard, *et al*.).

Environmental Partitioning

An EPIWIN Level III Fugacity Model was run using a log Kow=2.25, Henry's Law Constant of 0.000134 atm*m^{3}/mol, vapor pressure of 0.01 mmHg, melting point of 141°C, soil Koc of 72.9, and the default of equal distribution between compartments. The results show that DMT is expected to partition primarily to soil and water.

Compartment	Percent
Air	13.9
Water	34.4
Soil	51.6
Sediment	0.134

2.2.3 Predicted Environmental Concentration

Concentrations of DMT in the environment have not been monitored, but would be expected to be low. A Predicted Environmental Concentration (PEC) has not been calculated, since releases to water are expected to be insignificant due to its biooxidation in waste-water and current manufacturing processing in the U.S.

2.3 Human Exposure

2.3.1 Occupational Exposure

Less than 500 workers are estimated to be exposed at approximately 5-6 manufacturing and use sites in the U.S. Exposure may occur primarily during quality control sampling, loading or unloading tank cars or trucks, or when lines are disconnected for maintenance. Actual exposure is limited, because manufacturing and use processes are enclosed and continuous. Most manufacturing facilities (columns, tanks, lines) are located out-of-doors, with the processes being controlled in-doors via computer. Inhalation exposure is minimal, because of the very limited volatility, and for short periods (sampling, etc.). Accidental dermal contact is of concern primarily because of possible burns from molten liquid (melting point of 141 C^{o}). The use of personal

protective equipment (safety glasses, cap and leather gloves) is required whenever dermal exposure might occur.

2.3.2 Consumer Exposure

Since DMT is used solely as an industrial intermediate, no significant consumer exposure is anticipated.

2.3.3 Indirect Exposure via the Environment

Due to the low volatility of DMT and the manner in which it is produced and utilized, i.e., closed systems on-site industrial intermediate, exposure to non-industrial workers is essentially zero. Exposure through water is also of extremely low likelihood, as DMT is not utilized in consumer products. Furthermore, the amounts released into water from industrial sites are very low and DMT is readily degraded and does not bioaccumulate in aqueous organisms that could be consumed.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

Analog Justification

Data for dimethylterephthalate (DMT) is available for all SIDS health endpoints. However, for reproductive and developmental toxicity, the available data on DMT is not considered sufficient to support a conclusion that these endpoints have been completed. As a result, additional data from terephthalic acid (TPA) is being presented to support the conclusion that the reproductive and developmental toxicity endpoints have been completed. The use of TPA data for health endpoints is acceptable due to the principle that DMT metabolizes to form TPA.

3.1.1 Toxicokinetics, Metabolism and Distribution

Several studies conducted in rats, rabbits, and mice have all indicated that DMT is readily absorbed from the digestive tract and rapidly eliminated in the urine within 48-hours (Haskell Laboratory; Moffitt, A.E. Jr., et al., 1975; Heck, H. d.'A., 1980). Most of the absorbed DMT is metabolized to terephthalic acid (TPA) via hydrolysis, which sometimes combines with calcium to form TPA-Ca^{++} precipitates. In mice, the predominate metabolite was monomethyl terephthalate.

3.1.2 Acute Toxicity

Dimethyl terephthalate is of low toxicity following oral, inhalation, and dermal exposures. The oral LD_{50} in rats ranged from 4,390 to >6,590 mg/kg (Marhold, J.V., 1972; Krasavage, et al., 1973). Clinical signs consisted of slight to moderate weakness at all doses and slight tremors and atoxia at the highest doses (5,020 and 6,590 mg/kg). Respiratory irritation, mucosal hyperemia, increased excitation upon stimiulation, irregular breathing, and cyanosis were noted in rats following exposure to a hot vapor (LC_{50} >6 mg/L) (Sanina, Y.P. and Kochetkova, T.A., 1963). No deaths were reported in guinea pigs following dermal exposure to 5,000 mg/kg (Patty's Ind. Hyg. Tox., 1981).

3.1.3 Irritation

DMT applied topically to guinea pigs, mice (tails dipped into DMT solutions), and rabbits, was reported to be slightly irritating (Eastman Kodak, 1957; Eastman Kodak, 1963; Sanina, Y.P. and Kocketkova, T.A., 1963). In 2 different studies, DMT instilled in rabbit eyes had either no effect or induced a mild irritation (Eastman Kodak, 1957; Anonymous, 1986). A third study indicated a pronounced conjunctivitis was induced (time for return to normal was not reported) (Kamal' Dinova, Z.M., et al., 1962).

3.1.4 Sensitisation

Three different studies have all concluded that DMT does not induce allergic contact sensitization (Krasavage, W.J., et al., 1973; Patty's Ind. Hyg. Tox., 1981).

3.1.5 Repeated Dose Toxicity

Species* / Duration / Exposure Route	Dose / Exposure Level	NOEL/NOAEL	Reference
14 Days / Gavage	5,000 mg/kg/day	Not Determined.	Haskell Laboratory, MR-423-1.
14 Days / Diet	0, 0.5, 1.0, 1.5, 2, or 3% or 0, 5000, 10000, 15000, 20000, or 30000 ppm (Avg. dose for males was 660, 1320, 1890, 2260, and 2590 mg/kg/day, for females it was 638, 1277, 1790, 2290, and 3020 mg/kg/day.)	NOEL of 0.5% (660 mg/kg) in males and 1.0% (1277 mg/kg) in females	Chin, T.Y. *et al*., 1981
16 Days / Diet	5% or 10%	Not Determined	Haskell Laboratory, MR-423-1.
28 Days / Diet	0 or 5% or 50000 ppm(3,750 mg/kg/day)	Not Determined	Patty's Ind. Hyg. & Tox., 3rd Ed.
35-39 Days / Diet	500 mg/kg/day	NOEL was 500 mg/kg.	Prusakov, V.M., 1966
13 Weeks / Diet	0.5, 1.6 or 3% or 5000, 16000, or 30000 ppm	Not Determined	Vogin, E. E., 1972
13 Weeks / Diet	0.175, 0.25, 0.5, 1.0 or 2.0% or 1750, 2500, 5000, 10000, or 20000 ppm	A NOAEL of 0.5% for rats and 2.0% for mice.	Federal Register, 1981
96 Days / Diet	0, 0.25, 0.5 and 1.0% or 2500, 5000 or 10000 ppm (Avg. dose was 152, 313, and 636 mg/kg/day)	NOEL was 0.5% (313 mg/kg)	Krasavage, W.J., *et al*., 1973.
5 Months / Inhalation	1-4 or 40-70 mg/m^3 of DMT	Not Determined	Sanina, Y.P., 1963.
3 Months / Inhalation	0.0, 16.5, and 86.4 mg/m^3	NOAEL was 86.4 mg/m^3	Krasavage, W.J., *et al.*, 1973.
6 Months / Inhalation	15 mg/m^3	NOEL was 15 mg/m^3	Lewis, T.R. *et al*., 1982.
"Chronic" / Inhalation	0.08, 0.4 or 1 mg/m^3	Not Determined	Davidenko, A.V. *et al*., 1982.
"Chronic" / Inhalation	0.08, 0.4 or 1 mg/m^3	Not Determined	Davidenko, A.V. *et al*., 1984.
10 Days and 2.5 Months / Subcutaneous	2 g/kg (10 days) 1 g/kg (2.5 months)	NOEL was 2 g/kg	Slyusar, M.P., 1964.

* All studies were conducted in rats, while the NCI study also included mice and the Lewis study also included guinea pigs.

Numerous studies, mostly using rats, have been conducted to evaluate the affects of DMT following repeat exposures from various administration routes including oral (gavage and dietary), inhalation, and subcutaneous injections. Oral exposure studies have ranged in length from 2 to 13 weeks. Inhalation exposure studies of DMT dust have been conducted for up to 6 months in duration with a NOEL of 15 mg/m^3 (highest level evaluated) without evidence of any types of effect (Lewis, T.R. *et al*., 1982). The only target organ identified in oral exposure studies was that of the urinary tract. However, the observed toxicity was not the result of a direct DMT effect, but was mediated through indirect mechanisms. When DMT is administered in high doses it may induce the formation of renal and bladder crystals and calculi. The mechanism by which this occurs is through its metabolism to terephthalic acid (TPA) and the formation of TPA-Calcium precipitates. The

physical presence of these crystals and calculi leads to hematuria and to thickening of the bladder wall. The minimum dose level and exposure length at which these effects have been reported are 1.5% (1890 mg/kg; NOEL was 1790 mg/kg) and greater dietary concentrations for 14 days (Chin, T.Y. *et al*., 1981). Crystals were noted as being present in 12/16 males and 6/16 females fed DMT in their diet at a level of 3% for 28 days (Vogin, E. E., 1972). However, and for reasons that are unknown, crystal formation and hematuria are not consistently observed in all repeat dose studies. It was not noted in a 14-day gavage exposure study at 5,000 mg/kg (Haskell Laboratory), in two different studies of at least 28 days with dose levels of 5% (diet; Patty's Ind. Hyg. & Tox., 3rd Ed.) or 500 mg/kg (gavage) (Prusakov, V.M., 1966), or in two 13-week studies with maximum dietary exposure levels of either 1.0 or 2.0% (Krasavage, W.J., *et al.*, 1973, and Federal Register 1981). In addition, this phenomenon was not observed in the 2-year carcinogenicity study where DMT was present in the diet at 2.5 and 5% (Federal Register, 1981). The primary effect noted in these latter oral studies that did not develop calculi, or from administering DMT via other exposure routes, was a nonspecific decrease in body weight gain without any histological evidence of toxicity.

3.1.6 Mutagenicity

The results from several bacterial mutagenicity assays (Ames) have all indicated DMT is not mutagenic (Zeiger, E., et al., 1982; Zieger, E., et al., 1985; Kozumbo, W.J., et al., 1982; Monarca, S., et al., 1991; Monarca, S., et al., 1989; Elmore, E. and Fitzgerald, M.P., 1990). Negative results were also the norm 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, S., et al., 1989; Monarca, S., et al., 1991; Loveday, K.S., et al., 1990). These studies utilized mouse hepatocytes, Chinese hamster embryo cells, HeLa cells, and human lymphocytes. Negative in vivo studies include a sex-linked recessive lethality tests in *Drosophila* and one of two micronuclei studies in mice (Foureman, P., et al., 1994; Shelby, M.D., 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 vehicle (see dossier for full discussion) (Goncharova, R.I., *et al.*, 1988).

3.1.7 Carcinogenicity

DMT was evaluated for carcinogenic potential in a 2-year bioassay (Federal Register, 1981). This study, conducted by the National Cancer Institute of the United States, evaluated DMT dietary exposure levels of 2.5 and 5.0% (2,500 and 5,000 ppm) in rats and mice. These exposure levels did not affect body weight or survival, or induce any clinical signs of toxicity. No increases in tumors were noted in rats of either sex or female mice. An increase in lung tumors in male mice was considered equivocal.

3.1.8 Toxicity for Reproduction

Effects on Fertility

Reproductive toxicity was evaluated by exposing male rats to diets containing 0.25, 0.50, or 1.0% DMT for 115 days (Krasavage, W.J., *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 through lactation. No signs of toxicity were observed in either the male or female parental animals. Pups born to parents fed 0.5 and 1.0% DMT had significantly lower average body weights at weaning when compared to the controls. The NOEL was 1.0% (636 mg/kg/day) for parents and 0.25% (152 mg/kg/day) for their offspring. This effect on the offspring was likely due to exposure to DMT through lactation and having access to the mother's food, and hence it is a primary toxicity from DMT exposure. In a one-generation reproduction study, no adverse effects on fertility were noted

in adult rats fed up to 5% terephthalic acid (TPA) in the diet (CIIT 1982). Both maternal and post-natal effects occurred in the 2% and 5% groups. The NOAEL for maternal toxicity and for the F1 offspring was 0.5% (240 to 307 mg/kg), while the NOAEL for reproductive effects was >5.0% (2480-3018 mg/kg) TPA in the diet. There were increased postnatal deaths on Day 1 (fetotoxicity) and decreased survivability to Day 21. Several large litters of pups were lost to dams suffering obvious signs of maternal toxicity. Several of these dams did not allow the pups to nurse or attend to the litters. Unscheduled deaths occurred during the postweaning period in the 5% groups and was associated with a very high incidence of renal and bladder calculi. Weanling animals exhibit a higher incidence of calculi compared to adults consuming the same dietary level of terephthalic acid. This can be explained by the large amount of feed consumed in relation to body weight for young animals experiencing their initial growth spurt. Weanling animals are not more sensitive to TPA toxicity when the results are expressed on a mg/kg basis.

Developmental Toxicity

The potential for DMT to induce developmental toxicity in rats has been evaluated following an inhalation exposure to DMT at 1 mg/m^3 and after gavage exposure to 1,000 mg/kg throughout gestation (Krotov, Y.A. and Chebotar, N.A., 1972, and Hoechst 1986). In addition, inhalation exposures to terephthalic acid (TPA), the primary metabolite of DMT, at exposure levels up to 10 mg/m^3 have been assessed during days 6-15 of gestation in rodents (Amoco Corporation, 1989 and Ryan, *et al.*, 1990). No abnormal developmental effects and no pre- or post-implantation losses were noted in any study.

3.1.9 Experience with Human Exposure

There were only a few isolated reported instances in the literature in which possible effects from DMT exposure to humans were evaluated. In one, an oily paste containing 80% DMT showed no irritant effects 24 hours after 10 applications to human skin (Massmann, W., 1966). In another, no adverse effects were reported in workers exposed to high concentrations of DMT (Korbakova, A.I., 1964). While in a third study, a moderate leukocytosis was found in workers involved in the synthesis of DMT (Kamal'dinova, Z.M., et al., 1962). However, it was noted that these workers were also exposed to other chemicals.

3.2 Initial Assessment for Human Health

Workers

Airborne emissions consist primarily of dust or fumes. Product is normally handled in closed systems at all times. Air concentrations are predominately under 0.3 mg/m^3, higher air levels are associated with clean up and require use of respiratory protection devices. [0.3 mg/m^3 was the TWA value of twelve workers completing a full shift. Measured values ranged from 0.15 to 0.99 mg/m^3.]

Consumers

There is no known direct consumer exposure. Dimethyl terephthalate is used solely as an industrial intermediate. Residual DMT at an average of less than 1 ppm is found within polyethylene terephthalate (PET). DMT is esterified with ethylene glycol prior to incorporation into PET. This esterification process results in essentially no measurable DMT in finished product.

Those Exposed to the Environment

Based on the fact that DMT is an industrial intermediate manufactured and used in enclosed equipment with very low volatility, and is readily biodegradable, there is a very low potential for appreciable environmental exposure.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute toxicity studies to aquatic organisms indicate DMT is moderately toxic. Fish (Fathead minnow) had a 96h LC_{50} of 9.6 mg/L, in invertebrates it was 30 mg/L in *Daphnia,* >30 mg/L in the Sideswimmer (48h), >100 mg/L in the Flatworm (96h), and >30 mg/L in the snail (96h) (Eastman Kodak Co. 1977 and 1984). Similar toxicity values were seen in an acute algal toxicity study (72h NOEC 10.8 mg/L, biomass 72h EC_{50} 27.6 mg/L and growth 72h EC_{50} >32.3 mg/L) (Huls AG, 1993). Chronic toxicity studies were not available on any species.

The Predicted No Effect Concentration (PNEC) value for the aquatic environment would likely be 96 ug/L. The PNEC was estimated by applying a 100-fold safety factor to the most sensitive species (Fathead minnow; LC_{50} = 9.6 mg/L).

4.2 Terrestrial Effects

Based on its physical and chemical properties, DMT is not expected to accumulate in terrestrial environments. Although some soil bacteria were unable to catabolize DMT, most studies with soil microorganisms indicated that it could be used as a carbon source. If DMT is released into soil, it should have medium to high soil mobility.

Studies have been conducted assessing DMT effects on plant germination and seedling growth (Eastman Kodak Co. 1976 and 1984). Results showed that DMT had no effect on seed germination rates in lettuce at 1 mg/L, or in ryegrass and radish at 10 mg/L (Another study showed no effects in lettuce or radish at 30 mg/L). There was no effect on corn, marigold, and lettuce seedlings following exposure to DMT at concentrations of 33 mg/L, or on radish seedlings at 10 mg/L (Another study showed no effects on corn at 100 mg/L and radish, marigold, and lettuce at 1000 mg/L). It is important to point out that the robustness of the information associated with these studies questions their validity and overall usefulness.

4.3 Initial Assessment for the Environment

Aquatic Compartment

DMT is minimally soluble in water and has an overall low hazard potential in aquatic environments. Due to its main use as an industrial intermediate in the production of polymers, negligible quantities are released. Any DMT that does end up in this compartment has a very low potential to accumulate as it is readily removed through direct hydrolysis and microbial degradation (see 3.1.1). If a large quantity of material is accidentally released into the environment, it could lead to adverse consequences to some aquatic organisms. Both fish (Fathead minnow) and invertebrates (daphnia and sideswimmer) showed a moderate level of toxicity to it in lethality testing. Effects on algal growth were also noted at similar concentrations.

Terrestrial Compartment

Annual land releases of DMT from its manufacturing sites are essentially zero due to its end use as an industrial intermediate. Any material that does end up in terrestrial environments will be readily degraded through hydrolytic processes or be broken down by microbes. DMT had negligible effects on seed germination rates and seedling growth. Thus, DMT presents a very low concern in the terrestrial environment.

Atmospheric Compartment

Although atmospheric emissions have not been determined, such emissions are expected to be low. DMT's manufacture, use, and storage as an industrial intermediate take place within closed continuous equipment and DMT has very limited volatility. Available data indicate that vapor phase DMT will react with photochemically-produced hydroxyl radicals and lead to its removal. Thus, DMT presents a very low concern in the atmospheric environment.

5 CONCLUSIONS AND RECOMMENDATIONS

Conclusions

Dimethyl terephthalate is a high production volume chemical. It is produced in closed continuous equipment systems and is used primarily within its own manufacturing facilities in the synthesis of polyethylene terephthalate plastic and, to a lesser extent, dioctyl terephthalate. There is no known use of DMT in consumer or commercial products. When transported, it is shipped in bulk containers as a molten liquid. Thus, human exposures are very minimal and limited. The main exposure concern is that of direct physical burns due to accidental contact to molten DMT.

The physical-chemical properties of DMT which include a slow hydrolysis, photo-oxidation half-life of weeks, and stability in surface and ground water with half-lives of weeks, indicate this chemical is persistent enough in the environment to have a potential for causing an environmental hazard if there was the potential for significant environmental releases. This chemical is moderately toxic to fish, daphnid, and green algae. However, it is not expected to bioaccumulate in fish and is not expected to biomagnify via food chains.

Results from acute and repeat dose studies indicate DMT is of a low order of toxicity. In addition, given the weight of the evidence, DMT does not appear to be mutagenic or genotoxic, nor was it deemed to be a carcinogen based on 2-year feeding studies. Studies on DMT and the metabolite TPA indicate no evidence of developmental or reproductive toxicity. The primary toxicity manifested in laboratory animals was due to a secondary effect from its metabolism to TPA and the subsequent formation of renal crystals or calculi. Based on urinary solubility of Ca-TPA, human urine would become saturated with Ca-TPA at a TPA concentration of approximately 8-16 mM. Assuming an average urine volume formation of 1.5 L/day and that DMT is metabolized solely to TPA. The amount of DMT that would have to be absorbed in order to achieve a concentration of 8 mM in 1.5 L of urine, is 2,400mg/day (Heck, H. d'A. and Tyl, R.W., 1985; mw=194.2 x 8 mM x 1.5 L urine/day).

Recommendations

It is recommended that DMT be considered as low priority for further work.

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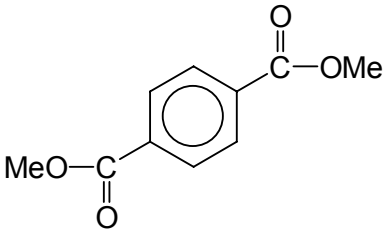
SIDS DOSSIER

Dimethyl terephthalate

CAS No. 120-61-6

Sponsor Country: United States

SIDS PROFILE

1.01 A.	**CAS No.**	120-61-6
1.01 C	**CHEMICAL NAME**	Dimethyl Terephthalate
1.01 D.	**CAS DESCRIPTOR**	
1.01 G.	**STRUCTURAL FORMULA**	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	
1.7	**USE PATTERN**	Used only as an industrial intermediate for the manufacture of polyethylene terephthalate and dioctyl terephthalate
1.9	**SOURCES AND LEVELS OF EXPOSURE**	(a) Human exposure is limited primarily to the workplace and can occur during sampling. (b) Environmental releases are low as a result of bulk storage and handling, closed system manufacture and use, and handling as a molten liquid with very low vapor pressure.
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)	SIDS testing required: None.	

SIDS SUMMARY DATA

CAS NO: 120-61-6		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	Y	N	N	Y	N	Y	N
2.4	Vapor Pressure	Y	N	N	Y	N	Y	N
2.5	Partition Coefficient	Y	N	N	Y	N	Y	N
2.6	Water Solubility	Y	N	N	Y	N	Y	N
	pH and pKa values	NA	NA	NA	NA	NA	NA	NA
2.12	Oxidation: Reduction potential	NA	NA	NA	NA	NA	NA	NA
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	Y	N	N	Y	N	Y	N
3.1.2	Stability in water	Y	N	N	Y	N	Y	N
3.2	Monitoring data	N	N	N	N	N	N	N
3.3	Transport and Distribution	Y	N	N	Y	Y	Y	N
3.5	Biodegradation	Y	N	N	Y	Y	Y	N
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	Y	N	N	Y		Y	N
4.2	Acute toxicity to Daphnia	Y	N	N	Y		Y	N
4.3	Toxicity to Algae	Y	N	Y	Y		Y	N
4.5.2	Chronic toxicity to Daphnia	N						N
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	Y	N	N	Y		Y	N
4.6.3	Toxicity to Birds	N						N
OTHER ECOTOXICITY STUDIES RECEIVED								

TOXICITY								
5.1.1	Acute Oral	Y	N	N	Y		Y	N
5.1.2	Acute Inhalation	Y	N	N	Y		N	N
5.1.3	Acute Dermal	Y	N	N	Y		Y	N
5.4	Repeated Dose	Y	N	N	Y		Y	N
5.5	Genetic Toxicity in vitro	Y	N	N	Y		Y	N
	Gene mutation	Y	N	N	Y		Y	N
	Chromosomal aberration	Y	N	N	Y		Y	N
5.6	Genetic Toxicity in vivo	Y	N	N	Y		Y	N
5.8	Reproduction Toxicity	Y	N	N	Y		Y	N
5.9	Development/Teratogenicity	Y	N	N	Y		N	N
5.11	Human Experience	Y	N	N	Y		Y	N
OTHER TOXICITY STUDIES RECEIVED								

1.01 SUBSTANCE INFORMATION

A. CAS-Number **120-61-6**

B. Name (IUPAC name) 1,4-Benzenedicarboxylic acid, dimethyl ester

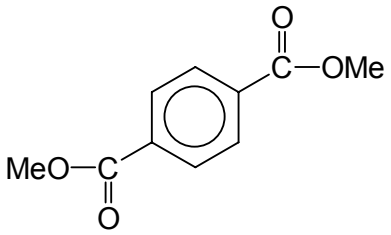
C. Name (OECD name) Dimethyl terephthalate

D. CAS Descriptor (where applicable for complex chemicals) Not applicable in this case

E. EINECS-Number **204-411-8**

F. Molecular Formula **$C_{10}H_{10}O_4$**

G. Structural Formula (indicate the structural formula in smiles code, if available**)**



H. Substance Group (if possible, only for petroleum products, see HEDSET Explanatory note)

Not Applicable

I. Substance Remark (indicate the substance remark as prescribed in the EINECS Inventory, if possible)

J. Molecular Weight 194.19

1.02 OECD INFORMATION

A. Sponsor Country: United States of America

B. Lead Organization U.S. Environmental Protection Agency

Contact person: Mr. Oscar Hernandez
Director, Risk Assessment Division

Address: Office of Toxic Substances (7403)
U S Environmental Protection Agency
401 M Street SW
Washington, DC 20460
Telephone (202) 260-1835
Fax (202) 260-1216

C. Name of responder (Information on a responder should be provided when companies respond to Lead Organization or SIDS Contact Points)

Name: James A. Deyo D.V.M., Ph.D., D.A.B.T.
Technical Associate
Product Safety and Stewardship
Address: Eastman Chemical Company
Kingsport, TN 37662-5280

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance
Element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; Organometallic [ ]; petroleum product [ ]

B. Physical State (at 20^{o} C and 1.013 hPa)
Gaseous [ ]; liquid [ ]; solid [X]

C. Purity (indicate the percentage by weight/weight)
99.9% (Eastman Chemical Company)

1.2 Synonyms

dimethyl 1,4,-benzenedicarboxylate
dimethyl p-benzenedicarboxylate
dimethyl p-phthalate
methyl 4-carbomethoxybenzoate
methyl p-(methoxycarbonyl)benzoate
terephthalic acid, dimethyl ester
DMT

1.3 IMPURITIES (indicate CAS No., chemical name (IUPAC name is preferable), percentage, if possible EINECS number)

(a) Methyl (p-formyl) benzoate – max. specification limit 40 ppm

(b) Methyl hydrogen terephthalate – max. specification limit 225 ppm

1.4 ADDITIVES (e.g. stabilizing agents, inhibitors, etc. Indicate CAS No. chemical name (IUPAC) name is preferable), Percentage, if possible EINECS Number), the component of The UVCB (Substance with no defined composition) should Be indicated here)

None

1.5 QUANTITY (Information on production or import levels should be provided in Figures or ranges (e.g., 1,000-5,000, 5,000-10,000 tonnes, etc.) per responder or country and the date for which those ranges apply should be given. For EEC Member states only indicate the Community import figure. Give an estimation of the global production quantity

in the remarks field. Information on the number of producers in the country and the source of information should also be described in the remarks field)

Total annual North American nameplate (maximum capacity) production capacity is estimated for 2004 at 1,917,000 mt or 4.23E9 pounds (SRI Consulting Jan. 2000).

Total annual worldwide nameplate production capacity is estimated for 2004 at 4,936,000 mt or 1.09E10 pounds (SRI Consulting Jan. 2000).

1.6 LABELLING AND CLASSIFICATION (If possible, enter information on labeling and classification such as labeling and classification system, existence of specific limit, symbols, nota, R-Phrases and S-Phrases of EC Directive 67/548/EEC, See HEDSET Explanatory note.)

1.7 USE PATTERN

A. General

Type of Use: Industrial intermediate used to manufacture polyethylene terephthalate, and dioctyl terephthalate

Category: Non-dispersive use; Chemical industry use as intermediate

B. Uses in Consumer Products

None

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

ACGIH: None

1.9 SOURCES OF EXPOSURE

Dimethyl terephthalate is manufactured from the oxidation of p-xylene by an enclosed, continuous process. It is handled as a molten liquid, possessing low vapor pressure, transferred through closed lines to heated storage tanks. Transport of molten DMT is via tank car or truck. DMT is reacted further on site or other industrial sites to manufacture polyethylene terephthalate polyester and dioctyl terephthalate.

There is limited potential for industrial exposure, which would occur primarily during quality control sampling. Short periods (one worker per day at one plant up to one- hour per 8-hour shift) of exposure to vapor can also occur during the loading of trailers and tank cars. The primary dermal hazard would be thermal burns from the hot molten DMT during sampling or line disconnection. The required wearing of leather gloves during these operations minimizes the possibility of dermal contact and burns.

Because DMT is handled as a melt with low vapor pressure in enclosed manufacturing, storage and processing systems the potential for environmental release is limited.

2.1 MELTING POINT: 141° C (286° F)
Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Dimethyl terephthalate, BG Chemie Toxicological Evaluations 1 Potential Health Hazards of Existing Chemicals, Springer-Verlag, Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona

2.2 BOILING POINT: 280° C (543° F); 288° C (550° F)
Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: 1.) Dimethyl terephthalate, BG Chemie Toxicological Evaluations 1 Potential Health Hazards of Existing Chemicals, Springer-Verlag, Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona
2.) The Merck Index (12) and USEPA OPPT/ICB internal database

2.3 SPECIFIC GRAVITY (water = 1): 1.1 – solid; liquid (molten) 1.05

Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

2.4 VAPOR PRESSURE: 133 mbar (100 mmHg) at 208° C; 1.15 mmHg at 93° C; 0.01 mmHg at 25° C
Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: 1.) Material and Safety Data Sheet; Eastman Chemical Company
2.) Aldrich MSDS found ONLINE
3.) USEPA OPPT/ICB internal database

2.5 PARTITION COEFFICIENT: logP = 2.25; P = 178
Method:
GLP: Yes [ ]
No [X]
Comments: Obtained from HSDB No. 2580

Reference: Hansch, C., Leo, A., D. Hoekman. (1995) Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society; 69.

2.6 WATER SOLUBILITY:

A. **Solubility:** 1.) 28.7 mg/L (20^{o} C); 2.) 19 mg/L (25^{o} C); 3.) 140 mg/L (25^{o} C); 4.) 500 mg/L (20^{o} C); 5.) 37.2 mg/L (25^{o} C)

Method: 1.) EEC A6-MOS/PHC/019
GLP: Yes [X]
No [ ]
Comments: Methods used for studies 2-5 are unknown or are believed to be estimations.
Reference: 1.) Montefibre Spa; IUCLID
2.) Kuhne, R. *et al.* (1995) Chemosphere 30:2061-77 ; HSDB No. 2580.
3.) USEPA OPPT/ICB EPIWIN
4.) Dimethyl terephthalate, BG Chemie Toxicological Evaluations 1 Potential Health Hazards of Existing Chemicals, Springer-Verlag, Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona
5.) Eastman Kodak Company Environmental Safety Data Sheet; HAEL No. 77-0311 and 80-0056; unpublished data.

B. **pH Value, pKa Value:** NA

2.7 FLASH POINT: 153^{o} C (308^{o} F)

Method: Cleveland, open cup
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

2.8 AUTOIGNITION TEMPERATURE: 519^{o} C (965^{o} F)

Method: ASTDM D-2155
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

2.9 FLAMMABILITY: Non-flammable

2.10 EXPLOSIVE PROPERTIES

A. **Sensitivity to mechanical impact:** Insensitive
Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

B. **Lower explosive limit:** 0.000033 mg/L
Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

2.11 OXIDIZING PROPERTIES: Not an oxidizer

2.12 OXIDATION/REDUCTION POTENTIAL

N/A

2.13 ADDITIONAL DATA

A. **Physical Form:** Solid; Liquid (molten)

Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

B. **Color:** White

Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

C. Odor: Slight

Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

D. Vapor density (Air = 1): 6.7

Method:
GLP: Yes [ ]
No [X]
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

3.1 STABILITY

3.1.1 PHOTODEGRADATION

A. **Test substance:** Dimethyl terephthalate
Test type: Hydroxyl radical and ozone reactivity
Test method:
GLP: Yes [ ]
No [X]
Test result: DMT was reactive toward OH• radicals with a half-life of approx. 3-days, and was unreactive toward ozone.
Comments: The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
Reference: Brown, S.L., *et al*., 1975.

B. **Test substance:** Dimethyl terephthalate
Test type: Photooxidation half-life
Test method:
GLP: Yes [ ]
No [X]
Test result: The half-life was determined to be 4.7 to 46.6-days.
Comments: The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
Reference: Howard, P.H., *et al*., Page 465.

3.1.2 STABILITY IN WATER

A. **Test substance:** Dimethyl terephthalate
Test type: Alkoxyradical reactivity
Test method:
GLP: Yes [ ]
No [X]
Test result: DMT was not reactive toward RO_2• radicals in aqueous media.
Comments: The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
Reference: Brown, S.L., *et al*., (1975).

B. **Test substance:** Dimethyl terephthalate
Test type: Hydrolytic half-life
Test method: Neutral water at 25^{o} C
GLP: Yes [ ]
No [X]
Test result: The half-life was 321-days
Comments: The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.

Reference: Mabey, W. and Mill, T. (1978) "Critical review of hydrolysis of organic compounds in water under environmental conditions" J. Phys. Chem. Ref. Data. 7(2):383-415. In "Health and Environmental Effects Profile for Dimethyl Terephthalate" (1984) EPA/600/X-84/152.

C. **Test substance:** Dimethyl terephthalate
Test type: Half-life
Test method:
GLP: Yes [ ]
No [X]
Test result: The half-life was estimated to be 1 to 4-weeks for surface water and 2 to 8-weeks for ground water.

Comments: The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
Reference: Howard, P.H., *et al*., Page 464.

D. **Test substance:** Dimethyl terephthalate
Test type: Log sediment organic content/water partition coefficient
Test method: Calculated
GLP: Yes [ ]
No [X]
Test result: $K_{oc} = 2.49$
Comments: Information predates GLP regulations
Reference: Mabey, W.R., *et al*., (1984).

3.1.3 STABILITY IN SOIL

Test substance: Dimethyl terephthalate
Test type: Half-life
Test method:
GLP: Yes [ ]
No [X]
Test result: The half-life was estimated to be 1 to 4-weeks.
Comments: The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
Reference: Howard, P.H., *et al*., Page 464.

3.2 MONITORING DATA (ENVIRONMENT)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 Distribution and Fugacity Calculation

Test type: Fugacity Modelling
Method: Level III Mackay-type, fugacity based models obtained from Trent University's Modeling Center. Specific model: Equilibrium Conctnration model (EQC) Level 3 model, version 1.01.
Remark: Default values were assumed for environmental compartment descriptions, dimensions, and properties, advective and dispersive properties. Chemical-specific parameters included Henry's Law Constant of 0.000134 atm*m^3/mol, vapor pressure of 0.01 mm Hg, melting point of 141 °C, log Kow of 2.25, and soil Koc of 72.9. These values were obtained by the model either through estimates or measured database values.
Distribution: Air (13.9%), Water (34.4%), Soil (51.6%), Sediment (0.134%).
Reliability: (2) valid with restrictions.
Source: Meylan, W. 2000. User's Guide for EPIWIN, Version 3.05.
Syracuse Research Corporation. North Syracuse, NY. March, 2000.

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

3.5 BIODEGRADATION

A. **Test substance:** Dimethyl terephthalate
Test type: Chemical oxygen demand (aerobic)
Test medium:
Test method:
GLP: Yes [ ]
No [X]
Test result: COD = 1.70 g oxygen/g
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

B. **Test substance:** Dimethyl terephthalate
Test type: Bacterial degradation
Test medium: Activated sludge
Test method: Media was inoculated under aerobic conditions with 100 mg/l of DMT.
GLP: Yes [ ]
No [ ]
? [X]
Test result: Theoretical BOD = 84%
Comments: Japanese MITI test
Reference: Chemicals Inspection and Testing Institute (1992); Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan. Japan Chemical Industry Ecology – Toxicology and Information Center. ISBN 4-89074-101-1.

C. **Test substance:** Dimethyl terephthalate
Test type: Biological Degradation
Test medium: River water and Seawater
Test method: DMT at levels of 5, 40, and 50 ppm was cultivated for 3-days.
GLP: Yes [ ]
No [X]

Test result: Degradation rate was 100% in river water and 49, 38, and 27% in seawater at the low, medium and high dose levels.
Comments: None
Reference: Kondo, *et al*., (1988).

D. **Substance:** Dimethyl terephthalate
Test type: Bacterial degradation
Test medium: Mineral salts medium
Test method: 6000 ppm of test compound was incubated (shaken at 30^{o} C) with Pseudomonas acidovorans 256-1 for 40-days.
GLP: Yes [ ]
No [X]
Test result: No degradation was noted.
Comments: None
Reference: Kurane, R., *et al*., (1977).

E. **Test substance: Dimethyl terephthalate**
Test type: Bacterial degradation
Test medium:
Test method: DMT was incubated with a Rhodococcus species isolated from soil.
GLP: Yes [ ]
No [X]
Test result: The isolated bacterial species was capable of utilizing DMT as its sole carbon source completely degrading the molecule.

Comments: Similar results were obtained by Samsonova and Slizen using Rhodococcus erythropolis.
Reference: Ninnekar, H.Z., *et al*., (1985) and Slizen Z.M. (1989).

F. **Test substance: Dimethyl terephthalate**
Test type: Bacterial degradation
Test medium: Soil and wastewater containing DMT.
Test method: In one experiment, soil containing 100 mg DMT/400 g was inoculated with Rhodococcus erythropolis. In the second study, aerated wastewater from a DMT manufacturing facility was inoculated with 10% of a bacterial medium containing Rhodococcus erythropolis.
GLP: Yes [ ]
No [X]
Test result: DMT in soil was completely degraded after approximately 10-days. The inoculated wastewater degraded the DMT 100% after 212-hours.
Comments: None
Reference: Samsonova, A.S., *et al*., (1989).

G. **Test substance:** Dimethyl terephthalate
Test type: Bacterial degradation
Test medium:
Test method: DMT was incubated with Bacillus sp. isolated from garden soil.
GLP: Yes [ ]
No [X]

Test result: The isolated bacterial species was capable of utilizing DMT as its sole carbon source.
Comments: None
Reference: Sivamurthy, K., *et al*., (1989).

H. **Test substance:** Dimethyl terephthalate
Test type: Fungal degradation
Test medium:
Test method: Test compound was incubated with *Aspergillus niger* to assess its degradation potential.
GLP: Yes [ ]
No [X]
Test result: DMT was metabolized through monomethyl terephthalate, terephthalate, and protocatechuate with. Analysis of media using UV spectroscopy indicated 58% of the DMT was taken up in 144-hours.
Comments: None
Reference: Ganji, S.H., *et al.*, (1995).

I. **Test substance:** Dimethyl terephthalate
Test type: IC_{50}; Secondary waste water
Test medium:
Test method: 5-Hours
GLP: Yes [ ]
No [X]
Test result: IC_{50} = >5000 mg/L
Comments: Information predates GLP regulations
Reference: Material and Safety Data Sheet; Eastman Chemical Company

3.6 BOD, COD OR RATIO BOD/COD

3.7 BIOACCUMULATION

Test substance: Dimethyl terephthalate
Test type: Log bioconcentration factor (BCF)
Test method: Calculated by method of Kenaga (1980)
GLP: Yes [ ]
No [X]
Test result: BCF = 1.21
Comments: Information predates GLP regulations
Reference: In "Health and Environmental Effects Profile for Dimethyl Terephthalate" (1984) EPA/600/X-84/152.

4.1 ACUTE/PROLONGED TOXICITY TO FISH

A. **Test substance:** Dimethyl terephthalate
Test species: *Pimephales promelas* (Fathead minnow)
Test method: 96 hr, static
GLP: Yes [ ]
No [X]
Test results: LC_{50} = 9.6 mg/L, NOEC = 3 mg/kg
Comments: 30 mg/l was lethal to all fish
Reference: Eastman Kodak Co. 1984, unpublished data

B. **Test substance:** Dimethyl terephthalate
Test species: *Pimephales promelas* (Fathead minnow)
Test method: 96 hr, static
GLP: Yes [ ]
No [X]
Test results: LC_{50} = 45 mg/L
Comments: None
Reference: Eastman Kodak Co.1977, unpublished data

C. **Test substance:** Dimethyl terephthalate
Test species: *Pimephales promelas* (Fathead minnow)
Test method: 96 hr
GLP: Yes [ ]
No [ ]
? [X]
Test results: LC_{50} = 14.2 mg/L
Comments: None
Reference: Material Safety Data Sheet; DuPont Chemicals

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. **Test substance:** Dimethyl terephthalate
Test species: *Daphnia magna* (Water flea)
Test method: 96 hr, static
GLP: Yes [ ]
No [X]
Test results: LC_{50} = > 100 mg/L
Comments: None
Reference: Eastman Kodak Co. 1977, unpublished data

B. **Test substance:** Dimethyl terephthalate
Test species: *Daphnia magna* (Water flea)
Test method: 48 hr, static
GLP: Yes [ ]
No [X]
Test results: EC_{50} = >30 mg/L
Comments: Exposure to 30 mg/L induced 40% immobility
Reference: Eastman Kodak Co. 1984, unpublished data

C. **Test substance**: Dimethyl terephthalate
Test species: *Daphnia magna* (Water flea)
Test method: 48-hr
GLP: Yes [ ]
No [ ]
? [X]
Test results: LC_{50} = 30.4 mg/L
Comments: None
Reference: Material Safety Data Sheet; DuPont Chemicals

D. **Test substance:** Dimethyl terephthalate
Test species: *Dugesia tigrina* (Flatworm)
Test method: 96 hr, static
GLP: Yes [ ]
No [X]
Test results: LC_{50} = >100 mg/L
Comments: None
Reference: Eastman Kodak Co. 1977, unpublished data,

E. **Test substance:** Dimethyl terephthalate
Test species: *Helisoma trivolvis* (Snail)
Test method: 96 hr, static
GLP: Yes [ ]
No [X]
Test results: LC_{50} = >100 mg/L
Comments: None
Reference: Eastman Kodak Co. 1977, unpublished data

F. **Test substance:** Dimethyl terephthalate
Test species: *Helisoma trivolvis* (Snail)
Test method: 96 hr, static
GLP: Yes [ ]
No [X]
Test results: LC_{50} = >30 mg/L; NOEC 3 mg/L
Comments: None
Reference: Eastman Kodak Co. 1984, unpublished data

G. **Test substance:** Dimethyl terephthalate
Test species: *Gammarus fasciatus* (Sideswimmer)
Test method: 96 hr, static
GLP: Yes [ ]
No [X]
Test results: EC_{50} = >30 mg/L; NOEC 3 mg/L
Comments:
Reference: Eastman Kodak Co. 1984, unpublished data

4.3 TOXICITY TO AQUATIC PLANTS

A. **Test substance:** Dimethyl terephthalate; purity 99.99%
Test species: *Scenedesmus subspicatus* (algae)
Test method: Directive 88/302 EEC; 72-hr
GLP: Yes [X]
No [ ]

Test results:	Biomass	Growth Rate
	EC_{50}: 27.6 mg/L	EC_{50}: >32.3 mg/L
	EC_{10}: 14.3 mg/L	EC_{10}: 20.1 mg/L
	NOEC: 10.8 mg/L	NOEC: 10.8 mg/L

Comments: No analytical monitoring, concentrations were nominal. For the growth rate endpoint, an EC_{50} was not reached at the highest concentration tested (32.3 mg/L). At test beginning pH was 7.7-8.0 and it was 8.2-9.1 at conclusion. The estimated algal toxicity EC_{50} using ECOTOX software is 1.5 mg/L (96-hr).
Reference: Huls AG, unpublished data; Report AW-301; 1993

4.4 TOXICITY TO BACTERIA

Not available

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

Not available

4.5.1 CHRONIC TOXICITY TO FISH

Not available

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Not available

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1. TOXICITY TO SOIL DWELLING PLANTS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

A. **Test substance:** Dimethyl terephthalate

Test species: Ryegrass, Radish, Lettuce
Test method: 7-Day germination exposures to concentrations of 0, 1, 10, 100, or 1000 mg/L. There were 80 seeds used for each exposure test level and 40 seeds for control.
GLP: Yes [ ]
No [X]
Test results (No Adverse Effect Conc.): 10 mg/L (Rye grass, Radish), 1 mg/L (Lettuce)
Comments: Data predate GLP regulations
Reference: Eastman Kodak Co. 1976, unpublished data

B. **Test substance:** Dimethyl terephthalate

Test species: Ryegrass, Radish, Lettuce
Test method: Germination
GLP: Yes [ ]
No [X]
Test results (No Adverse Effect Conc.): 10 mg/L Rye grass, 30 mg/L (Radish, Lettuce)
Comments: Data predate GLP regulations; test duration and dose levels are unknown
Reference: Eastman Kodak Co. 1984, unpublished data

C. **Test substance:** Dimethyl terephthalate
Test species: Corn, Marigold, Lettuce, Radish
Test method: 1-week phytotoxicity to seedlings. Exposures to DMT concentrations of 0, 100, and 1000 mg/L. There were 10 corn seedlings and 20 seedlings for the other species per exposure level.
GLP: Yes [ ]
No [X]
Test results (No Adverse Effect Conc.): >1000 mg/L (Radish, Marigold, Lettuce), >100 mg/L, (Corn,)
Comments: Data predate GLP regulations
Reference: Eastman Kodak Co. 1976, unpublished data

D. **Test substance:** Dimethyl terephthalate
Test species: Corn, Marigold, Lettuce, Radish
Test method: Seedling growth
GLP: Yes [ ]
No [X]
Test results (No Adverse Effect Conc.): >10 mg/L (Radish), >33 mg/L (Lettuce, Corn, Marigold)
Comments: Data predate GLP regulations; test duration and dose levels are unknown
Reference: Eastman Kodak Co. 1984, unpublished data

E. **Test substance:** Wastewater from a DMT manufacturing facility
Test species: Jowar, Mung, Bajra
Test method: Plant germination effects were assessed using wastewater treated in the laboratory with a mixed culture of Pseudomonas sp., Aeromonas sp., Arthrobacter sp., and Bacillus sp.
GLP: Yes [ ]
No [ ]
? [X]
Test results (No Adverse Effect Conc.): The treated wastewater had no effect on germination rates in any species tested.
Comments: None
Reference: Goud, H.D., *et al*., (1990).

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

A.

Type:	LD_0 []; LD_{100} []; LD_{50} [X]; LDL_0 []; Other []
Species/strain:	Rat/Long-Evans Hooded
Value:	>6,590 mg/Kg
Method:	Oral doses of 0, 3000, 3900, 5020 or 6590 mg/Kg DMT were administered to groups of 3-6 male rats as a 20% solution in corn oil. The animals were observed for clinical signs of toxicity and mortality for 14-days. After 14-days of observations, the animals were euthanized, autopsied, and examined for gross pathology and histopathology.
GLP:	Yes []; No [X]; ? []
Test substance:	Commercial (Eastman Organic Chemicals)
Remarks:	No mortality was observed during the 14-day post-treatment period. Clinical signs of toxicity were limited to slight to moderate weakness at all dose levels and slight tremors and ataxia at the 5,020 and 6,590 mg/Kg dose levels. No signs of gross or histopathological changes due to systemic toxicity were noted at necropsy.
Reference:	Krasavage *et al*., 1973.

B.

Type:	LD_0 []; LD_{100} []; LD_{50} [X]; LDL_0 []; Other []
Species/strain:	Rat
Value:	4,390 mg/Kg
Method:	Unknown
GLP:	Yes []; No [X]; ? []
Test substance:	DMT
Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference.
Reference:	Marhold, J.V., 1972.

5.1.2 ACUTE INHALATION TOXICITY

Type:	LC_0 []; LC_{100} []; LC_{50} [X]; LCL_0 []; Other []
Species/strain:	Rat
Value:	>6 mg/L
Method:	A two-hour inhalation exposure was conducted using a 100-liter chamber. DMT vapors (reported at 100-110°C; however, melting point is 142° C) were generated using a hot plate and introduced into the chamber containing six animals. Chamber temperature was between 25 and 29° C. Upon cooling, the vapors form a light, fluffy aerosol. Chamber concentrations were not reported. A control chamber was used but not described.
GLP:	Yes []; No [X]; ? []
Test substance:	DMT

Remarks:	Respiratory irritation was evident along with mucosal hyperemia, increased excitation upon stimulation, irregular breathing, and cyanosis in animals exposed to the hot vapor. No deaths were reported. Interpretation of the study is limited by the lack of detail in the study report.
Reference:	Sanina, Y.P. and Kochetkova, T.A., 1963.

5.1.3 ACUTE DERMAL TOXICITY

Type:	LD_0 []; LD_{100} []; LD_{50} [X]; LDL_0 []; Other []
Species/strain:	Guinea Pig
Value:	>5,000 mg/Kg
Method:	Unknown
GLP:	Yes []; No [X]; ? []
Test substance:	DMT
Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference.
Reference:	Patty's Industrial Hygiene and Toxicology, 3rd Revised Edition, 1981.

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

A.	**Species/strain:**	Guinea Pig
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating []; Slightly irritating [X]; Not irritating []
	Method:	DMT was moistened with water and applied (1 and 2 g/Kg) to two animals using gauze. It was held in place with a rubber cuff for 24-hours.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	Slight redness, no edema
	Reference:	Unpublished data, Eastman Kodak Co., (1957).
B.	**Species/strain:**	Guinea Pig
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating [X]; Slightly irritating []; Not irritating []
	Method:	Solid DMT was moistened with water and applied (0.25 – 1.0 g/Kg) to three animals using a gauze. It was held in place with a rubber cuff for 24-hours.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	Erythema and slight to moderate edema were noted with sparse hair at 2-weeks.
	Reference:	Unpublished data, Eastman Kodak Co., (1963).

C.	**Species/strain:**	Mouse
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating []; Slightly irritating [X]; Not irritating []
	Method:	The tails of mice were inserted into test tubes containing a suspension of DMT (conc. not reported) in 5% starch for 2-hours/day for 10-days.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	Repeated submersion of the tails induced a transient (1-2 hr duration) slight hyperemia after the third exposure. Behavioral changes were noted after 6 submersions. Tails and behavior were reported to be normal by Day 12. Interpretation of the study is limited by the lack of detail in the study report.
	Reference:	Sanina, Y.P. and Kocketkova, T.A., 1963.
D.	**Species/strain:**	Rabbit
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating []; Slightly irritating [X]; Not irritating []
	Method:	The skin of rabbits (free of fur) were exposed to a suspension of DMT (conc. not reported) in 5% starch for 2-hours, after which the test material was washed away with warm water. Up to 10 applications were performed.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	Repeated application to the skin induced a slight irritation after 3-days that was reported to have disappeared on Day 4. A pigmentation was noted after 10 applications. The skin was reported to be normal by Day 12. Interpretation of the study is limited by the lack of detail in the study report.
	Reference:	Sanina, Y.P. and Kocketkova, T.A., 1963.

5.2.2 EYE IRRITATION/CORROSION

A.	**Species/strain:**	Rabbit
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating []; Slightly irritating []; Not irritating [X]
	Method:	Unknown
	GLP:	Yes []; No [X]; ?[ ]
	Test substance:	DMT
	Remarks:	No damage or irritation was noted
	Reference:	Unpublished data, Eastman Kodak Co., (1957).
B.	**Species/strain:**	Rabbit
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating []; Slightly irritating [X]; Not irritating []

	Method:	500 mg of DMT was placed in the eyes for 24-hours.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Anonymous, 1986; RTECS 1988.
C.	**Species/strain:**	Unknown
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating []; Slightly irritating [X]; Not irritating []
	Method:	Unknown
	GLP:	Yes []; No [X]; ? [ ]
	Test substance:	DMT
	Remarks:	A pronounced irritating effect on the mucous membranes of the eyes was induced. The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Kamal' Dinova, Z. M., *et al.*, 1962.
D.	**Species/strain:**	Rabbit
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating []; Slightly irritating [X]; Not irritating []
	Method:	Two drops of DMT suspended in a starch solution were instilled.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	Interpretation of the study is limited by the lack of detail in the study report.
	Reference:	Sanina, Y.P. and Kochetkova, T.A., 1963.
E.	**Species/strain:**	Rabbit
	Results:	Highly corrosive []; Corrosive []; Highly irritating []; Moderately irritating []; Slightly irritating [X]; Not irritating []
	Method:	Unknown
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Patty's Industrial Hygiene and Toxicology, 2nd Edition, 1963.

5.3 SKIN SENSITIZATION

A.	**Type:**	"Drop-on"
	Species/strain:	Guinea Pig

	Results:	Sensitizing []; Not Sensitizing [X]; Ambiguous []
	Method:	A drop-on skin sensitization study was conducted with 0.5 ml of a 1% solution of DMT in acetone:dioxane:guinea pig fat (7:2:1) dropped onto the rump area of 10 animals. Primary irritation was determined at 24 and 48-hours post-dosing. Three additional dose applications occurred over the next five-days and then the animals remained unexposed for 3-weeks. Challenge doses were applied to the right and left shoulders the next two-weeks, respectively. Erythema and edema were scored on a scale of 0 to 4.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT (Eastman Organic Chemicals).
	Remarks:	Neither primary irritation nor skin sensitization was induced by DMT.
	Reference:	Krasavage, W.J. *et al*., 1973.
B.	**Type:**	"Footpad"
	Species/strain:	Guinea Pig
	Results:	Sensitizing []; Not Sensitizing [X]; Ambiguous []
	Method:	0.5 ml of a 1% solution of DMT in acetone:dioxane:guinea pig fat (7:2:1) dropped onto the rump area of 10 animals. Primary irritation was determined at 24 and 48-hours post-dosing. After one-week, a mixture of the dosing compound (a 1% solution of DMT in acetone:dioxane:guinea pig fat (7:2:1) was mixed with whole heparinized rabbit blood (1%) for 1 to 3-hours and 0.05 ml 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 by drop-on one-week later. Sensitization scores were recorded at 24 and 48-hours after the challenge dose.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT (Eastman Organic Chemicals).
	Remarks:	Neither primary irritation nor skin sensitization was induced by DMT.
	Reference:	Krasavage, W.J., *et al*., 1973.
C.	**Type:**	Unknown
	Species/strain:	Guinea Pig
	Results:	Sensitizing []; Not Sensitizing [X]; Ambiguous []
	Method:	Animals received 5,000 mg/kg dermal exposure of DMT.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT (Eastman Organic Chemicals).
	Remarks:	DMT induced slight irritation but no sensitization reaction. The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Patty's Industrial Hygiene and Toxicology, 3rd Revised Edition, 1981.

5.4 REPEATED DOSE TOXICITY

A.	**Species/strain:**	Rat
	Sex:	Unknown
	Route of administration:	Oral, gavage
	Exposure period:	14-Days
	Frequency of treatment:	5-Days/week
	Post-exposure observation period:	At least 11-days (Actual length is not noted)
	Dose:	5,000 mg/kg/day
	Control group:	Yes []; No []; No data [X]; Concurrent no treatment []; Concurrent vehicle []; Historical []
	NOEL:	Not determined
	LOEL:	5,000 mg/kg/day
	Results:	While no rats died during the 10-day exposure dosing period, 5 of 6 animals died with pathology indicative of starvation by Day 11 after exposure had ended. During the exposure period, animals exhibited transient signs of discomfort and progressive weight loss. There was no hematuria or polyuria, nor was there any crystalline precipitates observed in the urine. There were no calculi or crystals in the bladder or kidneys of the rats at necropsy.
	Method:	Rats were administered DMT for 10-days in a two-week period.
	GLP:	Yes []; No []; ? [X]
	Test substance:	DMT
	Remarks:	Interpretation of the study is limited by the lack of detail in the report.
	Reference:	Haskell Laboratory, Du Pont Co., unpublished data, MR-423-1.
B.	**Species/strain:**	Rat (weanling)/F-344
	Sex:	Male and Female
	Route of administration:	Oral, feed
	Exposure period:	14-Days
	Frequency of treatment:	7-Days/week
	Post-exposure observation period:	None
	Dose:	0, 0.5, 1.0, 1.5, 2, or 3% (females: 638, 1277, 1790, 2290, and 3020 mg/kg; males: 660, 1320, 1890, 2260, and 2590 mg/kg) DMT
	Control group:	Yes [X]; No []; No data []; Concurrent no treatment [X]; Concurrent vehicle []; Historical []
	NOEL:	0.5% (660 mg/kg) (males); 1.0% (1277 mg/kg) (females)
	LOEL:	-
	Results:	Average BW of the animals consuming the 1.5% and above was decreased on study Days 6-8 and

12-14 (postnatal Days 34-36 and 40-42) in females and 1.0% in males. Decreases in BW were accompanied by reduced feed consumption (possible palatability problems). There was no effect on water consumption at any dose. The incidence of bladder calculi in males from the 0, 0.5, 1.0, 1.5, 2.0, and 3.0% DMT dietary groups were 0, 0, 0, 35, 72, and 100%, respectively. The incidence of bladder calculi in females from the 0, 0.5, 1.0, 1.5, 2.0, and 3.0% DMT dietary groups were 0, 0, 0, 0, 36, and 47%, respectively. Grossly observable 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 terephthalic acid (TPA) with 5-7% protein. Phosphate levels were low, in contrast to bladder calculi from animals treated directly with terephthalic acid. Neither oxalate, nor uric acid, was found in the calculi. An acidic urinary pH was believed to have induced the hypercalciuria, a characteristic of urolithiasis in man. The higher urinary concentrations of TPA from DMT in the diet (when compared to similar dietary concentrations of TPA) explained the higher incidence of urinary calculi from the DMT diets than from comparable levels of TPA in the diet. Urinary phosphate levels were decreased in the animals consuming the DMT diet and explained why phosphate was present only at very low levels in the bladder calculi in those animals.

Method: Rats (13-18/sex/dose group) were fed DMT diets for a period of two-weeks. Individual body weights and total feed and water intake per cage were collected. At necropsy, urine was collected directly from the bladder for pH measurement, and concentrations of "stone-forming" materials were determined. The urinary system was examined grossly for presence of macroscopic calculi. Any calculi were collected, dried, weighed and analyzed. This study also evaluated terephthalic acid (TPA) at similar dietary levels.

GLP: Yes []; No []; ? [X]

Test substance: DMT (Eastman Chemical, Lot No. A9A), ground and filtered through a No. 35 sieve**.**

Remarks: Weanling rats are probably more sensitive to the induction of bladder calculi than adults due to their very high feed consumption rates relative to body weight.

	Reference:	Chin, T.Y. *et al*., 1981.
C.	**Species/strain:**	Rat
	Sex:	Unknown
	Route of administration:	Oral, feed
	Exposure period:	5% (16-Days); 10% (>16-Days)
	Frequency of treatment:	7-Days/week
	Post-exposure observation period:	None
	Dose:	5 and 10%
	Control group:	Yes []; No []; No data [X]; Concurrent no treatment []; Concurrent vehicle []; Historical []
	NOEL:	Not determined
	LOEL:	5%
	Results:	Hematuria was observed in all rats at some time during the study. All rats from the group consuming a diet containing 5% DMT and killed on Day 17 had bladder stones and 3 of 5 had minute calculi in their kidneys. Four of six rats consuming the 10% DMT diet died between study Days 2 and 17. With the exception of one rat that died on Day 2, all animals consuming the 10% DMT diet exhibited hematuria and had urinary bladder or kidney stones.
	Method:	Rats were fed DMT in their diets at a rate of 5 and 10%. The 5% dose group was sacrificed after 16-days.
	GLP:	Yes []; No []; ? [X]
	Test substance:	DMT
	Remarks:	Interpretation of the study is limited by the lack of detail in the report.
	Reference:	Haskell Laboratory, Du Pont Co., unpublished data, MR-423-1.
D.	**Species/strain:**	Rat
	Sex:	Males
	Route of administration:	Oral, feed
	Exposure period:	28-Days
	Frequency of treatment:	7-Days/week
	Post-exposure observation period:	None
	Dose:	5% DMT in diet; 3,750 mg/kg/day
	Control group:	Yes [X]; No []; No data []; Concurrent no treatment [X]; Concurrent vehicle []; Historical []
	NOEL:	Not determined
	LOEL:	5%
	Results:	DMT animals consumed approx. half the amount of feed as controls and lost approx. 40 grams over the 28-day period, while controls gained approx. 135 grams. One DMT animal died on Day 16. At no time point did hematological parameters show

		any abnormalities. Also histopathological examination of selected tissues did not reveal any lesions attributable to DMT exposure. After 28-days on test diet the four remaining animals were returned to the control diet. Interestingly, these four animals died the first night upon return to the control diet.
	Method:	Diets containing DMT were fed to rats (5/dose) for 28-days. Body weights and feed consumption were recorded and hematological parameters were collected at the beginning, middle and end of the feeding period.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	Interpretation of the study is limited by the lack of detail in the report.
	Reference:	Patty's Industrial Hygiene and Toxicology, 3rd Edition, 1981.
E.	**Species/strain:**	Rat
	Sex:	Unknown
	Route of administration:	Oral, feed
	Exposure period:	35 to 39-Days (500 mg/kg) and longer for the lower dose levels
	Frequency of treatment:	7-Days/week
	Post-exposure observation period:	None
	Dose:	0.5, 7.5, and 500 mg/kg/day
	Control group:	Yes [X]; No []; No data []; Concurrent no treatment [X]; Concurrent vehicle []; Historical []
	NOEL:	500 mg/kg/day
	LOEL:	-
	Results:	Rats exposed to 500 mg/kg/day for 35 to 39-days or 0.5 and 7.5 mg/kg/day for a longer duration did not differ from control animals.
	Method:	Animals were administered DMT in their diets for various time periods.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Prusakov, V.M., 1966.
F.	**Species/strain:**	Rat
	Sex:	Male and Female
	Route of administration:	Oral, feed
	Exposure period:	13-Weeks
	Frequency of treatment:	7-Days/week

	Post-exposure observation period:	None
	Dose:	0.5, 1.6 or 3% DMT in diet
	Control group:	Yes []; No []; No data [X]; Concurrent no treatment []; Concurrent vehicle []; Historical []
	NOEL:	Not determined
	LOEL:	0.5%
	Results:	The incidence of bladder calculi in animals fed diets containing 3% DMT for 13-weeks was 12/16 and 6/16 in male and female rats, respectively. The incidence of bladder calculi in male rats fed diets containing 1.6% DMT was 1/19, and 2/19 in the 0.5% exposure group. Calculi were not noted in mid- and low-dose females. The incidence of moderate hyperplasia of the internal bladder epithelial lining in animals fed diets containing 3% DMT for 13-weeks was 11/16 and 7/16 in males and females, respectively. Of the animals fed the 3% DMT diet and developing hyperplasia of the bladder lining, calculi were found in 11/11 males and 6/7 females. There were no neoplastic changes.
	Method:	Rats (7-19/group) were fed DMT diets for 13-weeks.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Reference:	Vogin, E. E., 1972.
G.	**Species/strain:**	Rat and Mouse
	Sex:	Male and Female
	Route of administration:	Oral, feed
	Exposure period:	13-Weeks.
	Frequency of treatment:	7-Days/week
	Post-exposure observation period:	None
	Dose:	1750, 2500, 5000, 10000 or 20000 ppm
	Control group:	Yes [X]; No []; No data []; Concurrent no treatment [X]; Concurrent vehicle []; Historical []
	NOEL:	Rat 5000 ppm (NOAEL), Mouse 20000 ppm (NOAEL)
	LOEL:	-
	Results:	No compound-related effects were noted in the physical appearance, behavior, or feed consumption measures of either species. No deaths occurred in the rats. One male mouse at 2500, 5000, and 20000 ppm died during the study, and two females at 20000 ppm. Body weight gains of males fed 20000 ppm was 83% of controls. Body weight gains of females fed 10000 and 20000 ppm was 83% and 71% of their respective controls.

		There were no differences in body weight or body weight gain in the male and female mice receiving DMT in the diet. No gross lesions were observed in rats or mice at necropsy. Microscopic examinations of the livers from both species in all dose groups revealed diffuse hepatocellular swelling. Although this change was considered compound related, it was not manifested in a dose-related manner.
	Method:	Groups (10/sex) of rats and mice were fed DMT in their diets for 13-weeks. Physical appearance and behavior were noted and feed consumption and body weights were measured.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT
	Reference:	National Cancer Institute Technical Report Series, NCI-CG-TR-121, No. 121, 1979.
H.	**Species/strain:**	Rat/Long-Evans Hooded
	Sex:	Males
	Route of administration:	Oral, feed
	Exposure period:	96-Days
	Frequency of treatment:	7-Days/week
	Post-exposure observation period:	Till natural death
	Dose:	0, 0.25, 0.5 and 1.0% (152, 313, 636 mg/kg)
	Control group:	Yes [X]; No []; No data []; Concurrent no treatment [X]; Concurrent vehicle []; Historical []
	NOEL:	0.5% (313 mg/kg)
	LOEL:	-
	Results:	The only toxicological effect seen in the study was a reduced weight gain in the high dose animals. No toxicological effects on hematocrit, hemoglobin, white blood cell or differential counts were seen in any group. No dose-related changes were seen in BUN, SGOT, OCT, SAP, blood glucose, or serum protein values. Average body and relative and absolute liver and kidney weights of the experimental groups did not differ significantly from control weights. Microscopic examination of tissues from all organ systems revealed no morphologic evidence of any abnormalities that could be attributed to compound exposure.
	Method:	Weanling rats (30/group) were exposed to DMT in a basal diet. Ten animals from each group were sacrificed after 96-days, and tissue samples from

		all major organ systems were removed for histologic examination. Livers and kidneys were weighed for organ weight comparisons. Hematology and serum biochemistry's were conducted on Days 55 and 90. The remaining animals were placed back onto control diet for observation of potential long-term effects over the rest of their life.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT (Eastman Organic Chemicals, Cat. No. 6580).
	Reference:	Krasavage, W.J., *et al*., 1973.
I.	**Species/strain:**	Rat
	Sex:	Unknown
	Route of administration:	Inhalation
	Exposure period:	5-Months
	Frequency of treatment:	2-Hours/day
	Post-exposure observation period:	None
	Dose:	1-4 or 40-70 mg/m^3
	Control group:	Yes []; No []; No data [X]; Concurrent no treatment []; Concurrent vehicle []; Historical []
	NOEL:	Not determined
	LOEL:	1-4 mg/m^3
	Results:	At 1-4 mg/m^3, conjunctivitis, hypoactivity, a decrease in blood pressure, erythrocytopenia, reticulocytosis, leukopenia, and an increased electrical neuro-excitability was noted. At 40-70 mg/m^3, 30% mortality, rhinitis, depilation, dystrophic changes in the liver and kidneys, hemorrhage of the lungs, brain and myocardium, and hyperemia of the internal organs were reported.
	Method:	Inhalation exposure for five-months.
	GLP:	Yes []; No [X]; ?[]
	Test substance:	DMT
	Remarks:	Interpretation of the study is limited by the lack of detail in the study report.
	Reference:	Sanina, Y.P. and Kocketkova, T.A., 1963.
J.	**Species/strain:**	Rat/Long-Evans Hooded
	Sex:	Male
	Route of administration:	Inhalation
	Exposure period:	3-Months (58 exposure)
	Frequency of treatment:	4-Hours/day, 5-Days/week
	Post-exposure observation period:	Till natural death
	Dose:	0.0, 16.5, and 86.4 mg/m^3
	Control group:	Yes [X]; No []; No data []; Concurrent no treatment [X]; Concurrent vehicle [];

		Historical []
	NOEL:	16.5 mg/m^3
	LOEL:	-
	Results:	Nose rubbing, preening and blinking were noted soon after the start of DMT exposures of 86.4 mg/m^3. 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 on hematocrit, hemoglobin, white blood cell or differential counts were seen in any of the treated groups. No dose-related changes were seen in BUN, SGOT, OCT, SAP, blood glucose or serum protein values. Average body and relative and absolute liver and kidney weights of the treated animals sacrificed at study termination did not differ significantly from control weights. Microscopic examination of tissues from all organ systems examined revealed no morphologic evidence of abnormalities attributable to DMT exposure.
	Method:	Groups of rats (30/dose) were exposed to DMT "dust clouds" containing 0.0, 16.5, and 86.4 mg/m^3 for 4-hours per day for 58 exposures (excluding weekends and holidays) over a 3-month period using one cubic meter inhalation chambers (University of Rochester type). The in-chamber temperature was 24-26^o C. The dust-cloud of DMT entered the chamber from the top via the air supply stream and was exhausted from the bottom. Within 24-hours after the last exposure, 10 rats were sacrificed, and tissue samples from all major organ systems were processed for histologic examination. Hematology and serum biochemistry's were conducted on approximately Days 55 and 90. Livers and kidneys were weighted for organ weight comparisons. The remaining animals (20/group) were put on the control diet and were observed for long-term effects over the remainder of their life.
	GLP:	Yes []; No [X]; ? []
	Test substance:	DMT (Eastman Organic Chemicals, Cat No.6580).
	Reference:	Krasavage, W.J., *et al.*, 1973.
K.	**Species/strain:**	Rat and Guinea Pig
	Sex:	Unknown
	Route of administration:	Inhalation
	Exposure period:	6-Months.
	Frequency of treatment:	6-Hours/day, 5-Days/week
	Post-exposure observation period:	None

	Dose:	15 mg/m^3 (The amount of respirable DMT was only 5 mg/m^3)
	Control group:	Yes []; No []; No data [X]; Concurrent no treatment []; Concurrent vehicle []; Historical []
	NOEL:	15 mg/m^3 (NOEL).
	LOEL:	-
	Results:	There were no detectable effects on body weights, or routine clinical chemistry or urinalysis parameters. Gross and histopathological evaluations of tissues from these animals were within normal limits.
	Method:	Inhalation - Exposure 6-hours a day, 5-days a week, for 6-months to 15 mg/m^3 of DMT. The amount of respirable DMT was only 5 mg/m^3.
	GLP:	Yes []; No []; ? [X]
	Test substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Lewis, T.R. *et al*., 1982.
L.	**Species/strain:**	Rat
	Sex:	Unknown
	Route of administration:	Inhalation
	Exposure period:	"Chronic"
	Frequency of treatment:	Unknown
	Post-exposure observation period:	None
	Dose:	0.08, 0.4 or 1 mg/m^3
	Control group:	Yes []; No []; No data []; Concurrent no treatment []; Concurrent vehicle []; Historical []
	NOEL:	Not determined
	LOEL:	0.08 mg/m^3
	Results:	Exposure to 1 mg/m^3 caused a substantial increase in basal and dopamine-inducible activity of adenylate cyclase. No note-worthy change was seen after exposure to 0.08 or 0.4 mg/m^3. Exposure to DMT also induced a dose-dependent inhibition of phosphodiesterase. Acetylcholinesterase activity was also inhibited in the synaptosomal-mitochondrial fraction of the brain cortex, but no effect was noted in its activity in the microsomal membrane.
	Method:	Chronic inhalation exposure to 0.08, 0.4 or 1 mg/m^3 of DMT.
	GLP:	Yes []; No []; ? [X]
	Test substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the

		primary reference, and is limited by the lack of detail in the report.
	Reference:	Davidenko, A.V. *et al*., 1982.
M.	**Species/strain:**	Rat
	Sex:	Unknown
	Route of administration:	Inhalation
	Exposure period:	"Chronic"
	Frequency of treatment:	Unknown
	Post-exposure observation period:	None
	Dose:	0.08, 0.4 or 1 mg/m^3
	Control group:	Yes []; No []; No data [X]; Concurrent no treatment []; Concurrent vehicle []; Historical []
	NOEL:	Not determined.
	LOEL:	0.08 mg/m^3
	Results:	The chronic effect of DMT on rats induced a significant decrease in the uptake of radiolabeled noradrenaline by gray matter synaptosomes. At 0.4 mg/m^3, uptake was decreased 20%, while at 1 mg/m^3, the decrease was 51%. No effect was noted on monoamine oxidase or catecholamine-o-methyl transferase activities.
	Method:	Inhalation exposure to 0.08, 0.4 or 1 mg/m^3 of DMT
	GLP:	Yes []; No []; ? [X]
	Test substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Davidenko, A.V. *et al*., 1984.
N.	**Species/strain:**	Rat
	Sex:	Unknown
	Route of administration:	Subcutaneous
	Exposure period:	10-Days and 2.5-Months
	Frequency of treatment:	Once/day
	Post-exposure observation period:	None
	Dose:	10-Days at 2 g/kg (for 10-days) and for 1 g/kg (for 2.5-months)
	Control group:	Yes []; No []; No data [X]; Concurrent no treatment []; Concurrent vehicle []; Historical []
	NOEL:	2 g/kg for 10-days. Not determined for the 2.5-month period.
	LOEL:	-
	Results:	No significant effects were noted in any of the assessed parameters following 10-days of exposure to 2 g/kg of DMT. The only observation noted

	following a 2.5-month exposure period was reduced body weight gain.
Method:	Subcutaneous injection of DMT in 20% oil emulsions. Information on body weight, organ vitamin C content, hematology, serum protein, and cholinesterase activity were assessed.
GLP:	Yes []; No [X]; ? []
Test substance:	DMT
Remarks:	Interpretation of the study is limited by the lack of detail in the study report.
Reference:	Slyusar, M.P. and Cherkasov, I.A., 1964.

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

A -	**Type**:	Bacterial reverse mutation assay
	System of testing:	Species/strain: *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537
	Concentration:	3.3 to 333 µg/plate
	Metabolic activation:	With []; Without []; With and Without [X]; No data []
	Results:	
	Cytotoxicity conc.:	With metab. activation: 666 ug Without metab. activ.: 666 ug
	Precipitation conc.:	Not determined
	Genotoxic effects:	+ ? - With metab. activation: [] [] [X] Without metab. activ.: [] [] [X]
	Method:	Modified Ames *et al.*, (1975)
	GLP:	Yes []; No []; ? [X]
	Test Substance:	DMT (Aldrich; purity 99%)
	Remarks:	Procedure: Pre-incubation Plates/test: Unknown Activation system: S-9 was from Aroclor 1254-induced male SD rats and Syrian hamsters. Media: Histidine selective Number of replicates: 2
	Reference:	Zeiger, E., *et al.*, 1982. Zeiger, E., *et al.*, 1985.
B -	**Type:**	Bacterial reverse mutation assay
	System of testing:	Species/strain: *Salmonella typhimurium* TA98, TA100.
	Concentration:	Unknown
	Metabolic activation:	With []; Without []; With and Without [X]; No data []
	Results:	
	Cytotoxicity conc.:	With metab. activation: Unknown Without metab. activ.: Unknown

Precipitation conc.: Not determined

Genotoxic effects:

	+	?	-
With metab. activation:	[]	[]	[X]
Without metab. activ.:	[]	[]	[X]

Method: The standard Ames assay with major modifications (shifting of histidine and biotin from the top to the bottom agar and reducing the glucose concentration to 67.5 mg/plate in the bottom agar).

GLP: Yes []; No []; ? [X]

Test Substance: DMT

Remarks: Procedure: Unknown
Plates/test: Unknown
Activation system: S-9 was from Aroclor 1254-induced male SD rats
Media: Histidine selective
Number of replicates: Unknown

Reference: Kozumbo, W.J., *et al.*, 1982.

C - Type: Bacterial reverse mutation assay

System of testing: Species/strain: *Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537, and TA1538

Concentration: 0.5 - 5,000 µg/plate

Metabolic activation: With []; Without []; With and Without [X]; No data []

Results:

Cytotoxicity conc.: With metab. activation: 5,000 ug
Without metab. activ.: 5,000 ug

Precipitation conc.: Unknown

Genotoxic effects:

	+	?	-
With metab. activation:	[]	[]	[X]
Without metab. activ.:	[]	[]	[X]

Method: Ames *et al.*, (1975) with DMT dissolved in a mixture of DMSO and Tween 20 (29:1).

GLP: Yes []; No []; ? [X]

Test Substance: DMT (Italian PET plastic industry, purity not reported).

Remarks: Procedure: Unknown
Plates/test: Unknown
Activation system: S-9
Media: Unknown
No. replicates: Unknown

Reference: Monarca, S., *et al.*, 1991.
Monarca, S., *et al.*, 1989.

D - Type: Bacterial reverse mutation assay

System of testing: Species/strain: *Photobacterium phosphorium*

Concentration: Unknown

Metabolic activation: With []; Without [X]; With and Without []; No data []

Results:

Cytotoxicity conc.: With metab. activation: Unknown

Without metab. activ.: Unknown

Precipitation conc.: Unknown

Genotoxic effects:

	+	?	-
With metab. activation:	[]	[]	[]
Without metab. activ.:	[]	[X]	[]

Method: Mutatox™ Assay; This assay utilizes dark mutants that have lost the ability to produce light via repression of the operon responsible for luminescence. Luminescence can be restored (derepressed) via several mechanisms such as direct interaction with the repressor region or interference with synthesis of the repressor.

GLP: Yes []; No []; ? [X]

Test Substance: DMT (Aldrich; purity 99%)

Remarks: Procedure: Unknown
Plates/test: Unknown
Activation system: None
Media: Unknown
No. replicates: Unknown

Reference: Elmore, E. and Fitzgerald, M.P., 1990.

B. NON-BACTERIAL IN VITRO TEST

A - Type: DNA single-strand breaks

System of testing: Species/strain: Rat hepatocytes

Concentration: 0, 3.75, 7.50, or 15.00 µmole/ml equivalent to 0, 727.5, 1,455, or 2,910 µg/ml

Metabolic activation: With [X]; Without []; With and Without []; No data []

Results:

Cytotoxicity conc.: With metab. activ.: >2,910 µg/ml
Without metab. activation: NA

Precipitation conc.:

Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[X]
Without metab. activ.:	[]	[]	[]

Method: DMT was dissolved in a mixture of DMSO and Tween 20 (29:1). Rat hepatocytes were isolated by conventional methods. Cytotoxicity (trypan blue exclusion) was measured following a 1-hour incubation period. The remaining cells were lysed and DNA was isolated on filters and eluted at alkaline pH. DNA was measured in the eluted fractions by fluorometric determinations using a Hoechst 33258 dye. A positive finding is designated when the percent DNA retained on the control filter minus the percent DNA retained on the filters from each treatment group is greater than 20% at dose levels with greater than 70% viability.

GLP: Yes []; No []; ? [X]

Test Substance: DMT (Italian PET plastic industry, purity not reported)

Remarks: Procedure: Primary rat hepatocytes were used
Plates/test: Unknown
Activation system: Primary rat hepatocytes
Media: Unknown
No. replicates: Unknown

Reference: Monarca, S., *et al.*, 1991.
Monarca, S., *et al.*, 1989.

B - Type: DNA single-strand breaks

System of testing: Species/strain: SV40-transformed Chinese Hamster Embryo cell line (CO60 cells)

Concentration: 0, 3.75, 7.50, or 15.00 µmole/ml equivalent to 0, 727.5, 1,455, or 2,910 µg/ml.

Metabolic activation: With []; Without [X]; With and Without []; No data []

Results:

Cytotoxicity conc.: With metab. activation: NA
Without metab. activ.: >2,910 µg/ml

Precipitation conc.: Unknown

Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[]
Without metab. activ.:	[]	[]	[X]

Method: DMT was dissolved in a mixture of DMSO and Tween 20 (29:1). Cytotoxicity (trypan blue exclusion) was measured following a 1-hour incubation period. Cells were lysed and DNA was isolated on filters and eluted at alkaline pH. DNA was measured in the eluted fractions by fluorometric determinations using a Hoechst 33258 dye. A positive finding is designated when the percent DNA retained on the control filter minus the percent DNA retained on the filters from each treatment group is greater than 20% at dose levels with greater than 70% viability.

GLP: Yes []; No []; ? [X]

Test Substance: DMT (Italian PET plastic industry, purity not reported)

Remarks: Procedure: SV40-transformed Chinese Hamster Embryo cell line (CO60 cells).
Plates/test: Unknown
Activation system: None
Media: Unknown
No. replicates: Unknown
Other: Results of this test were not fully reported.

Reference: Monarca, S., *et al.*, 1991.
Monarca, S., *et al.*, 1989.

C - Type: Unscheduled DNA synthesis
System of testing: Species/strain: Human/Hela
Concentration: 5, 50, 500, 5,000 µg/ml
Metabolic activation: With []; Without []; With and Without [x]; No data []

Results:
Cytotoxicity conc.: With metab. activation: Unknown
Without metab. activ.: Unknown

Precipitation conc.: Unknown
Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[X]
Without metab. activ.:	[]	[]	[X]

Method: Induction of unscheduled DNA synthesis was measured in HeLa cells exposed to varying concentrations of DMT dissolved in a mixture of DMSO and Tween 20 (29:1). DMT exposures were conducted in PBS with or without S9 liver fractions. Following treatment and rinsing to remove residual material, the cells were incubated with or without hydroxyurea (HU) in culture media. Tritiated methylthymidine was added after 15 minutes and the incubations continued for three-hours. Radioactivity was then counted to determine the incorporation of the radiolabeled thymidine. Inhibition of DNA replication and synthesis by HU in the control and treated cultures was determined by comparing the ratio of counts from 1) control w/o HU ÷ control plus HU, and 2) treated w/o HU ÷ treated plus HU. Inhibition of DNA replication and synthesis by DMT exposure was determined by the ratio of treated w/o HU ÷ control w/o HU. The effect of HU on the induction of DNA repair in the presence of DMT was determined by the ratio of (treated plus HU ÷ treated w/o HU) divided by (control plus HU ÷ control w/o HU).

GLP: Yes []; No []; ? [X]
Test Substance: DMT (Italian PET plastic industry, purity not reported)
Remarks: Procedure: Hela cells
Plates/test: Unknown
Activation system: S-9 was from Aroclor induced SD rats
Media: Phosphate-buffered saline
No. replicates: Unknown
Reference: Monarca, S., *et al.*, 1991.
Monarca, S., *et al.*, 1989.

D - Type: Chromosomal aberration

System of testing: Species/strain: Human PBL
Concentration: 50-500 µg/ml
Metabolic activation: With []; Without [X]; With and Without []; No data []

Results:
Cytotoxicity conc.: With metab. activation: NA
Without metab. activ.: Unknown

Precipitation conc.: Unknown
Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[]
Without metab. activ.:	[]	[]	[X]

Method: Lymphocytes (at stage G_0 of the cell cycle) were incubated with DMT for 4-hours at 37^o C. DMSO was the solvent control and bleomycin was used as a positive control. Following DMT exposure, cells were cultured for 72-hours in RPMI media. Colcemid was added to the cultures 2-hours prior to harvesting. Coded slides were prepared and the cells were stained with a 4% Giemsa solution. Cells (100/subject) in metaphase were examined for frequency of chromatid and chromosomal gaps and breaks.

GLP: Yes []; No []; ? [X]
Test Substance: DMT (Italian PET plastic industry, purity not reported)
Remarks: Procedure: Human peripheral blood lymphocytes isolated from heparinized intravenous blood.
Plates/test: Unknown
Activation system: None
Media: RPMI 1640 supplemented with 20% fetal calf serum and phytohemagglutinin
No. replicates: Unknown
Reference: Monarca, S., *et al.*, 1991.
Monarca, S., *et al.*, 1989.

E - Type: Chromosomal aberration (micronuclei formation)
System of testing: Species/strain: Human PBL
Concentration: 50-500 µg/ml
Metabolic activation: With []; Without [X]; With and Without []; No data []

Results:
Cytotoxicity conc.: With metab. activation: NA
Without metab. activ.: Unknown

Precipitation conc.: Unknown
Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[]
Without metab. activ.:	[]	[]	[X]

Method: Lymphocytes were incubated with DMT and cultured in RPMI 1640 media. After 44-hours,

cytochalasin D was added and the cultures continued until 72-hours. After a mild hypotonic treatment, the cells were fixed and coded slides prepared for staining with Giemsa and scoring for micronuclei. One thousand cells were scored per subject for the presence of micronuclei.

GLP: Yes []; No []; ? [X]

Test Substance: DMT (Italian PET plastic industry, purity not reported)

Remarks: Procedure: Human peripheral blood lymphocytes isolated from heparinized intravenous blood.
Plates/test: Unknown
Activation system: None
Media: RPMI 1640 supplemented with 20% fetal calf serum and phytohemagglutinin
No. replicates: Unknown

Reference: Monarca, S., *et al.*, 1991.
Monarca, S., *et al.*, 1989.

F - Type: Unscheduled DNA synthesis (DNA amplification)

System of testing: Species/strain: Hamster/Syrian (embryo cells)

Concentration: 0, 2.5, 5.0, or 10.0 µg/ml

Metabolic activation: With []; Without [X]; With and Without []; No data []

Results:

Cytotoxicity conc.: With metab. activation: NA
Without metab. activ.: >10.0 µg/ml

Precipitation conc.: Unknown

Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[]
Without metab. activ.:	[]	[]	[X]

Method: Cells were grown in tissue flasks and plated onto microtiter plates. After 24-hours DMT (in DMSO) was added. After 96-hours of exposure, the cells were harvested and counted, and viability determined (trypan blue exclusion). AAV (adeno-associated virus) DNA content was detected by *in situ* hybridization. The survival index was determined by comparison to survival rates in the control wells. The amplification factor was calculated by comparing the extent of in situ hybridization of treated groups divided by the rate for the control group. A genotoxicity index was calculated by multiplying the survival index by the amplification factor and dividing the result by 100.

GLP: Yes []; No []; ? [X]

Test Substance: DMT (Italian PET plastic industry, purity not reported)

Remarks: Procedure: Syrian hamster embryo cells infected with adeno-associated virus (AAV type 2)

Plates/test: Unknown
Activation system: None
Media: Unknown
No. replicates: Unknown

Reference: Monarca, S., *et al.*, 1991.
Monarca, S., *et al.*, 1989.

G - Type: Gene mutation

System of testing: Species/strain: Mouse/L5178Y lymphoma cells (clone 3.7.2C.)

Concentration: 0-100 ug/ml

Metabolic activation: With []; Without []; With and Without [X]; No data []

Results:

Cytotoxic conc.: With metab. activ.: >100 ug/ml
Without metab. activ.: >100 ug/ml

Precipitation conc.: 75 ug/ml

Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[X]
Without metab. activ.:	[]	[]	[X]

Method: Increases in the frequency of 5-trifluorothymidine(TFT)-resistant cells due to mutational events occurring at the thymidine kinase locus following DMT exposure (50 µg/ml) was determined with and without S9 fraction. Dimethylformamide (1%) was used as the solvent carrier. The treatment period was 4 hours at 37^{o} C in a roller drum (10-15 rpm). Cells were retrieved by centrifugation and washed twice with growth media. The two-day expression and growth period was conducted with cell densities of $3x10^5$ cells/ml (20 ml of media on roller drum). After two-days, the cells were added to 90 ml of cloning media. Dishes containing the cells and cloning media were incubated for 11 to 12-days at 37° C with 5% CO_2/humidified air for colony development.

GLP: Yes []; No []; ? [X]

Test Substance: DMT (NTP Repository, 99% purity)

Remarks: Procedure: L5178Y mouse lymphoma cells (clone 3.7.2C.)
Plates/test: Unknown
Activation system: Aroclor 1254-induced male F344 rats
Growth media: RPMI 1640 medium supplemented with heat-treated horse serum (10% v/v), 220 µg/ml sodium pyruvate, 2 mM L-glutamine, 0.05% Pluronic F68 and gentamycin (50 µg/ml)
Treatment media: Fischer's growth medium with 5% heat-treated horse serum.

Cloning media: Growth media plus 0.35-0.40% agar and 3 µg/ml TFT
No. replicates: Unknown

Reference: Myhr, B.C. and Caspary, W.J., 1991.

H - Type: Chromosomal aberration and Sister chromatid exchange

System of testing: Species/strain: Chinese Hamster Ovary (CHO) cells

Concentration: 10 ug/ml

Metabolic activation: With []; Without []; With and Without [X]; No data []

Results:

Cytotoxic conc.: With metab. activ.: >10 ug/ml
Without metab. activ.: >10 ug/ml

Precipitation conc.: >10 ug/ml

Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[X]
Without metab. activ.:	[]	[]	[X]

Method: CHO cells were grown and treated under conditions similar to those described by Galloway *et al*., (1985). Aroclor-induced rat liver microsomal preparations were combined with cofactors and added as the metabolic activation system. Medium and solvent controls were used with each assay. Positive controls (Mitomycin C for use without the metabolic activation system and cyclophosphamide for use with the activation system) were also included. For sister chromatid exchange (SCE) experiments without metabolic activation, bromodeoxyuridine (BRDU) was added 2-hours after the addition of the control or test substance and the culture continued for 24-hours. Fresh medium with BRDU and colcemid replaced the previous media and the cultures continued for 2.5-hours. For SCE experiments with metabolic activation, serum free medium with cofactors, S9 fraction, and chemical were used for 2-hours and replaced with medium containing BRDU and the culture continued for 24-hours. Colcemid was added to the media and the cultures continued for 2.5-hours. The cells were then examined for cytotoxicity, harvested and fixed. Fluorescence-microscopy was then used to assess the frequency of metaphase cells and SCE. For experiments examining chromosomal aberrations without metabolic activation, media with either the control or test substance was used for 8-hours and then removed. Media containing colcemid replaced the previous media and the cultures continued for 2.5-hours. For experiments with metabolic activation,

serum free medium with cofactors, S9 fraction, and chemical were used for 2-hours, then the media removed and fresh media used for 8-hours. Colcemid was then added and incubations continued for 2-hours. Cells were harvested and slides prepared using a 5% Giemsa stain for five minutes. Two hundred cells per dose were scored for chromosomal aberrations.

GLP: Yes []; No []; ? [X]
Test Substance: DMT (NTP Repository, 99% purity).
Remarks: Procedure: CHO cells
Plates/test: Unknown
Activation system: Aroclor 1254-treated male SD rats
Media: McCoy's 5A (modified media) buffered with 20 mM HEPES and supplemented with 10% FBS, 2 mM L-glutamine, 50 IU penicillin, and 50 µg/ml streptomycin.
No. replicates: Unknown
Reference: Loveday, K.S., *et al.*, 1990.

I - Type: Transformation Assay
System of testing: Species/strain: Mouse BALB/c-3T3 cells
Concentration: 0.644 - 5.15 mM
Metabolic activation: With []; Without [X]; With and Without []; No data []

Results:
Cytotoxic conc.: With metab. activation: NA
Without metab. activ.: 5.15 mM
Precipitation conc.: Unknown
Genotoxic effects:

	+	?	-
With metab. activ.:	[]	[]	[]
Without metab. activ.:	[]	[X]	[]

Method: The transformation assay consisted of three components: a clonal survival assay, a co-culture clonal survival assay and a transformation assay. The first two were used to determine cytotoxic dose levels and determine effect of cell density on cytotoxicity. In the cell transformation portion, 18-20 vessels were seeded with 3.2×10^4 cells/vessel and exposed to 4 different levels of DMT for 48-hours. The number of type I-III transformed foci were identified using established criteria (3 phenotypic criteria: piling and overlapping cells, disorientation of cells at the periphery of the focus, and invasion of transformed cells into a contact-inhibited monolayer of WT cells. Two difficult technical problems arose. DMT was temperature sensitive and reacts with water. The solubility of the test material in the

media necessitated the use of a solubilizing agent, sonication of the media and heating to form a fine particulate suspension.

GLP: Yes []; No []; ? [X]
Test Substance: DMT
Remarks: Procedure: BALB/c-3T3 cells, (A31-1-13 clone)
Plates/test: 18-20/4 dose levels
Activation system: None
Media: Unknown
No. replicates: Unknown
Other: DMT was evaluated to have indeterminate activity in this assay due to the fact that the material was tested at levels that far exceeded its solubility in the culture medium.
Reference: Matthews, E.J., *et al*., 1993.

5.6. GENETIC TOXICITY IN VIVO

A.

Type: Sex-linked recessive lethality
Species/strain: *Drosophila melanogaster*/Canton-*S* (males)and *Basc* (females)
Sex: Female []; Male []; Male/Female [X]; No data []
Route of administration: Diet and injection
Exposure period: 72-Hours
Doses: 1,000 ppm (diet) and 400 ppm (injection)
Results:
Effect on mitotic Index or P/N ratio:
Genotoxic effects: + ? -
[] [] [X] Both exposure routes
Method: Males were fed DMT solutions for 72-hours and then mated to three virgin females for 3-days. After three-days, the exposed male was transferred to three virgin females for 3-days. This was repeated one additional time so that three broods were collected from each exposed male. The test was repeated using injections. To reduce the possibility of recovering multiple lethals from one male, no more than 100 F_1 females were mated over the three broods from any P_1 male. F_2 cultures were scored as presumptive lethals if the number of wild-type males were 0, 1, or <5% of the number of *Basc* males or *Basc*/+ females.

GLP: Yes []; No []; ? [X]
Test Substance: DMT (Aldrich 99% purity)
Remarks: None
Reference: Foureman, P., *et al.*, 1994.

B.

Type:	Chromosomal aberration (micronucleus assay)
Species/strain:	Mouse/B6C3F1
Sex:	Female []; Male [X]; Male/Female [X]; No data []
Route of administration:	intraperitoneal injection
Exposure period:	3-Days
Doses:	438 to 1,750 mg/kg
Results:	
Effect on mitotic index or P/N ratio:	Control= 65% and 1,750mg/kg = 72%
Genotoxic effects:	+ ? - [] [] [X]
Method:	Mice (5-7) were exposed by ip injection to DMT (in a corn oil vehicle) over 3 consecutive days. The dose level used was the highest practical given the solubility problems with the test material. Animals were euthanized with CO_2 24-hours after their last exposure. Bone marrow smears (2 per mouse) were prepared and fixed with absolute methanol and stained with acridine orange. Each slide was evaluated for the number of micronuclei in polychromatic erythrocytes among 2,000 polychromatic erythrocytes and percentage of polychromatic erythrocytes among 200 erythrocytes.
GLP:	Yes []; No []; ? [X]
Test Substance:	DMT (NTP Repository, 99% purity)
Remarks:	None
Reference:	Shelby, M.D., *et al.*, 1993.

C.

Type:	Chromosomal aberration (micronucleus assay)
Species/strain:	Mouse/(C57Bl/6j x CBA)F_1
Sex:	Female []; Male [X]; Male/Female [X]; No data []
Route of administration:	intraperitoneal injection
Exposure period:	1-Day
Doses:	0.20 to 1.00 mmole/kg
Results:	
Effect on mitotic index or P/N ratio:	Control= 41%, DMSO = 43% and 1 mmol/kg= 37%
Genotoxic effects:	+ ? - [X] [] []
Method:	A single 0.2 ml solution of DMT (dissolved in a DMSO vehicle) was injected intraperitoneally. The highest dose level used was limited due to the toxicity of the vehicle. Fifteen mice per exposure group were used, although lethality occurred in some animals, thereby reducing the sample sizes. Negative control groups (distilled water, or 0.2 ml

DMSO) and a positive control group (methylnitrosourea) were included. Mice were killed by cervical dislocation at 24, 48 and 72-hours post-treatment. Slides were prepared according to the method of Schmid (1976), dried at room temperature, and stained with May-Gruenwald and Giemsa stains. Polychromatic erythrocytes (1,000/mouse) were scored for the presence of micronuclei. After identifying 200 erythrocytes, the ratio of polychromatic erythrocytes to normochromatic erythrocytes was determined.

GLP: Yes []; No []; ? [X]

Test Substance: DMT (99% purity)

Remarks: The results of this study are particularly difficult to interpret. The data is not presented on a per mouse basis, but instead all of the data from the animals are lumped together as a group. Therefore, there is no mean and standard deviation for each group value. The distilled water negative control group (n=24) had a reported micronuclei frequency of 1.5%, although the time after treatment when this was determined was not reported. The use of DMSO as a solvent caused mortality in 21 of 270 mice after receiving either DMSO or DMSO and test material. The remaining live animals within each group were randomly selected to evaluate the micronucleus endpoint. The frequency of micronuclei in the DMSO negative control group decreases from 2.5% at 24-hours to 1.17% at 48-hours and further to 0.83% at 72-hours. The percentage of polychromatic erythrocytes in the DMSO solvent control group was significantly increased over the distilled water control group at 24-hours. Clearly the toxicity of DMSO was affecting the number of polychromatic erythrocytes and micronuclei in the DMSO solvent control group. All dose levels of DMT tested increased the frequency of micronuclei, although these findings were primarily restricted to the 24-hour observation point, coincidentally the time of greatest increase in micronuclei frequency due to the DMSO vehicle. The increased frequency of micronuclei at 48-hours were limited to the 3 highest dose levels tested and at 72-hours, the two highest dose levels tested. The highest dose was also considered to have caused bone marrow suppression. The pattern of the time course for micronuclei formation in the treated groups mimicked that observed for the DMSO vehicle

		control, suggesting an interaction between the two chemicals (DMSO and DMT) may have occurred. Therefore, poor study design and reporting along with solvent toxicity makes interpretation of this study problematic. The dose levels tested were much lower than those used in other mouse micronuclei studies with a corn oil vehicle (3 injections over 3-days; above) and the increased frequency of micronuclei due to DMT treatment is in contrast to the other negative mutagenicity and clastogenicity findings for this material.
	Reference:	Goncharova, R.I., *et al.*, 1988.
D.	**Type:**	Sex-linked dominant lethal assay
	Species/strain:	*Drosophila melanogaster*
	Sex:	Female []; Male []; Male/Female []; No data [X]
	Route of administration:	Ingestion from media
	Exposure period:	Unknown
	Doses:	Unknown (it was mentioned that the nutrient media was spiked with 0.3 mM of DMT)
	Results:	
	Effect on mitotic Index or P/N ratio:	NA
	Genotoxic effects:	+ ? - [X] [] []
	Method:	Unknown
	GLP:	Yes []; No [X]; ? []
	Test Substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Goncharova, R.I., *et al*., 1984.

5.7 CARCINOGENICITY

A.	**Species/strain:**	Rat/F344 and Mouse/B6C3F1
	Sex:	Female []; Male []; Male/Female [X]; No data []
	Route of administration:	Diet
	Exposure period:	2-Years
	Frequency of treatment:	7-Days/week
	Post Exposure observation period:	2-Weeks
	Doses:	0, 2,500, or 5,000 ppm DMT
	Control group:	Yes [X]; No []; No data []; Concurrent no treatment [X]; Concurrent vehicle []; Historical [X]

Results:

Diet containing DMT at the above mention dose levels did not affect body weights, feed consumption, clinical signs, or survival. The bioassay report was issued twice in 1979. The first report concluded that DMT was carcinogenic in male mice due to an increased incidence of lung tumors in the low- and high-dose groups when compared to the matched controls. The matched control rate of lung tumors agreed with the historical control rate reported from the laboratory that conducted the study. DMT did not produce an increased incidence of any tumor types among male and female rats or among female mice. A draft of the first report was considered for peer review and was approved as written and released. The staff of the Carcinogenesis Testing Program of the National Cancer Institute (NCI) re-examined the data and reached the conclusion that the historical control rate of tumors to which the matched control group was compared was inappropriate for comparison since the historical control male mice came from studies of less than two-years duration. Since lung tumors are a late appearing tumor, the historical control rate for mice less than two years old would be expected to be low compared to that found in mice at two-years. The NCI staff then re-issued the report using "matched" control male mice lung tumor rates derived from other cancer bioassays conducted in the same room as the DMT bioassay at approximately the same time. The other male mice control groups housed concurrently with the male mice from the DMT bioassay had incidences of lung adenoma/carcinomas of 10% (5/49), 13% (6/46), and 18% (9/49) versus 4% (2/49) in control male mice in the DMT bioassay. Therefore, the lung tumor incidence in the male mouse control group in the DMT bioassay was considered "inordinately low". In addition, the majority (18/22) of the primary lung tumors found in the concurrent controls, were present in mice that survived to 104-weeks. The DMT control male mice had a survival rate of 64% (32/50) at that time point, while 82% and 78% of the low- and high-dose male mice (respectively) survived to 104-weeks. The lower survival rate (at two-years) of male control mice in the DMT bioassay may have been responsible for the low lung tumor incidence in that group. The re-issued report concluded that "The variability

evidenced by these control groups prevents an outright conclusion that the 13/49 (27%) incidence of lung tumors observed in the high dose male group in the (DMT) study is associated with the administration of the chemical." The Technical Report Summary concludes that DMT was not carcinogenic for F-344 rats or B6C3F1 mice under the conditions of the test. The revised report only had the abstract, statistical analysis, discussion and summary sections modified. The section dealing with the murine pathology (page 36) has the following statement "Based on histopathologic examination, a dose-related increase in primary tumors of the lung in male B6C3F1 mice may have been associated with long-term dietary administration of dimethyl terephthalate under the conditions of this bioassay." It is only in the statistical analysis section of the mouse bioassay report that the results are discussed.

On June 23, 1981, the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors conducted a peer review of the two reports. The re-issued report had been issued without an evaluation by a scientific review panel and the first report was considered incorrect based upon the arguments presented in the re-issued report.

In June 1981, NTP began 1) A re-examination and validation of the original diagnoses of lung tumors in the male mice, 2) A data analysis using the diagnoses of the pathologist performing the validation, and 3) presentation of the findings to the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors. The following conclusions were made by the Subcommittee: The original incidence of lung tumor was confirmed, however, the stage of tumor progression (adenoma vs. carcinoma) was questioned. Therefore, an analysis of the data was performed that considered the total lung tumor incidence rather than considering adenomas and carcinomas separately. Statistical analysis was done using the diagnosis of the validation pathologist by NTP/IARC recommended methods. Statistical comparisons included the incidences in both matched control and pooled control male mice. The conclusions out of this review were that

a statistically significant increase in total lung tumors was found for the high-dose group using either the matched-control or pooled-control incidences. However, this finding was considered biologically equivocal due to the following reasons: Lung tumors are relatively common in B6C3F1 mice, and the rate of incidence in the historical controls ranges from 2 to 34 percent. The 27% incidence rate found in the high-dose male mice in the DMT bioassay was within the high limit of the control range. Total lung tumor incidence is not dependent upon the sex of the mice and female mice had lung tumor incidences comparable to control values. Therefore, the observed lung tumor incidence in the male mice was considered less likely to be due to DMT exposure. The overall effect of the report revision followed by the re-interpretation by NTP in 1981 has been considerable confusion regarding the bioassay conclusions.

Method: A cancer bioassay was conducted on groups of 50 animals/species/sex. DMT was consumed in the diet for 104-weeks, followed by a 2-week observation period. At the end of the observation period the animals were necropsied and tissues examined histologically.

GLP: Yes []; No []; ? [X]

Test Substance: DMT (Technical grade obtained from Eastman Chemical Company. Analyzed by melting point, thin layer chromatography, elemental analysis, infrared, ultraviolet, visible and nuclear magnetic resonance spectra.)

Remarks: DMT has also been suggested to be a bladder carcinogen based on the 2-year bioassay results of one of the primary DMT metabolites, terephthalic acid (TPA). This suggestion is based upon the ability of high dietary concentrations of DMT to cause bladder stone formation following metabolism of DMT to TPA and excretion of the TPA in the urine. However, the NCI bioassay demonstrated no such effect (i.e. bladder stone formation or increase in urinary tract tumors or pathology). A possible reason as to why bladder stone formation was not found in the NCI bioassay was that although the dietary concentration of DMT used in the two-year studies was 0.25% and 0.5% it was still not sufficiently high enough to induce their formation.

Reference:	Federal Register (1981) "Public Health Service: Reevaluation by the National Toxicology Program of Technical Report NCI-CG-TRI-121 Entitled Bioassay of Dimethylterephthalate for Possible Carcinogenicity" FR 46(238):60654-60657. National Cancer Institute Technical Report Series "Bioassay of Dimethyl Terephthalate For Possible Carcinogenicity" (CAS No. 120-61-6, NCI-CG-TR-121, No. 121, 1979, revised summary)

5.8 TOXICITY TO REPRODUCTION

Type:	Fertility [X]; One generation study []; Two generation study []; Other []
Species/strain:	Rat/Long-Evans Hooded
Sex:	Female []; Male []; Male/Female [X]; No data []
Route of administration:	Oral, feed
Exposure period:	Males 115-days, Females 6-days prior to mating throughout gestation, parturition and lactation
Frequency of treatment:	7-Days/week (diet)
Post Exposure observation period:	Through weaning
Premating exposure period:	Males: 115-Days Females: 6-Days
Duration of test:	Through weaning of F1 animals
Doses:	0.25, 0.50, or 1.0%
Control group:	Yes [X]; No []; No data[]; Concurrent no treatment [X]; Concurrent vehicle []; Historical []
NOEL Parental:	1.0%
NOEL F1 Offspring:	0.25%
NOEL F2 Offspring:	NA
Results:	No signs of toxicity were observed in either the male or female parental animals (P). No effects were observed on fertility, reproductive capacity, libido, pregnancy, gestation, litter size, or offspring viability due to consumption of DMT. Pups born to parents fed 0.5 and 1.0% DMT had significantly lower average body weights at weaning when compared to the controls.
Method:	Males were fed DMT diets for 115-days. These males were then mated with virgin females that had been on test diets for 6 days. After mating, the pregnant females were fed the DMT diets throughout gestation, parturition and lactation.
GLP:	Yes []; No [X]; ? []
Test Substance:	DMT (Eastman Chemical Company, Cat. No. 6580)
Remarks:	The decreased weights observed at weaning are believed to be due to lactation exposure to the

DMT or its metabolite, TPA and access to treated diet. Studies with TPA have demonstrated an increased incidence of renal and bladder calculi formation in weanling animals when compared to adults consuming the same dietary level of terephthalic acid. This apparent increased sensitivity can be explained by the large amount of feed consumed in relation to body weight for young animals experiencing their initial growth spurt. Weanling animals are not more sensitive to terephthalic acid toxicity when the results are expressed on a mg/kg basis.

Reference: Krasavage, W.J., *et al.*, 1973.

B.

Type	:	other; one-generation
Species	:	Rat
Sex	:	male and female
Strain	:	CD and Wistar
Route of administration	:	oral; in feed
Exposure period	:	paternal: 90 days prior to and throughout mating maternal: 90 days prior to mating, throughout mating, gestation, and lactation offspring: 51 days; from birth through lactation and 30 days post weaning
Frequency of treatment	:	daily; in feed
Duration of test	:	approximately 160 days
Doses	:	0.03, 0.125, 0.5, 2.0, and 5.0%
Remark	:	The approximated mg/kg doses based on average feed consumption and body weight during the 90 day pre-mating period were: CD(M): 14, 59, 240, 930, 2499 CD(F): 17, 67, 282, 1107, 2783 Wistar(M): 14, 61, 249, 960, 2480 Wistar(F): 19, 78, 307, 1219, 3018
Control group	:	yes; concurrent no treatment
NOAEL Parental	:	0.5% (CD; Wistar: 2.0%)
NOAEL Reproductive	:	>5.0% (CD and Wistar)
NOAEL F1 Offspring	:	0.5% (CD and Wistar)
Method	:	other
Year	:	1982
GLP	:	Yes (see remark)
Test substance	:	terephthalic acid
Remark	:	No specific test material supplier or purity of test material was noted. A manager of quality assurance signed off on the study report. However, the report did not contain a specific statement *per se* in regard to the study being conducted under GLP assurances.

Result : Parental Effects: Following 90 days of exposure to TPA, statistically significant decreases in food consumption were observed in CD females treated with 2% and 5%, and in both sexes of Wistars treated with 5%.
Body weights were statistically decreased after 13 weeks in both sexes of CD rats on 2% and 5% TPA diets, and in males exposed to 0.03%. This effect occurred in Wistars (both sexes) only at the 5% level. There were 5 deaths (3 CD females, 1 Wistar/sex) reported during weeks 4-13 in animals given 5% TPA in the diet.
During the one-generation component of the study 3 CD (1 male at 2.0%, 1/sex at 5.0%) and 4 Wistar female (2 at 5.0% and 2 at 0.03%) rats died.
There was no effect of treatment on fertility index and litter size.

Offspring Effects: There were no effects of treatment on litter size, sex ratio, or total number of offspring. While no control offspring were found dead on Day 0, 17 Wistar pups (1 at 0.03%, 2 at 0.125%, 1 at 0.5%, 12 at 2.0% (2 from one dam and 10 from another)) and 23 CD pups (1 at 0.5%, 7 at 2.0% (3 dams) and 15 at 5.0% (3 dams; with 11 from one of them)) were found dead. No statistical differences were noted in viability on Days 0, 1, or 21 in either strain. In CD rats, survivability on Day 21 was reduced in both sexes of offspring whose parents had been exposed to 5% TPA in the diet.

In Wistar rats, body weights of both sexes of offspring from dams given 5.0% were reduced at Day 1. On Day 21, body weight was reduced in both strains of offspring from dams that ingested 5% TPA in the diet. Increased postnatal deaths on Day 1 and decreased survivability to Day 21 were noted in the 2% and 5% groups. At these dose levels, several large litters of pups were lost to dams suffering obvious signs of toxicity. Several of these dams did not allow the pups to nurse or attend to the litters. These pups were noted not to have milk in their stomachs and presented clinically as being very weak. These dams were consuming dietary levels of TPA known to cause reduced feed consumption, diarrhea and gastric trichobezoars (hairballs) and induce the formation of renal and bladder calculi. Unscheduled deaths during the postweaning period (Day 21-51) were confined to the 5% TPA group (18 Wistar and 16 CD) and were associated with a very high incidence of renal and bladder calculi. Renal and bladder calculi were noted in all animals exposed to 5% that were necropsied at Day 21. Day 51 necropsy findings also reported a very high incidence of renal and bladder calculi and the histological sequelae of the presence of the calculi.

Test condition : This study contrasted the toxicity of TPA in two different strains of rats. Experimental conditions were identical for both. Rats 15-17 weeks of age (n=30) were grouped housed 3/cage for the first 90 days of exposure. Body weight and feed intake were determined weekly during this time period. On Day 91, breeding pairs (n=10/sex) were housed together for 2 weeks prior to being separated. On Day 0 (delivery) the number and viability of offspring were evaluated and

grossly examined. Offspring were recounted, sexed, and weighed on Day 1. These measurements were repeated at weaning on Day 21. After weaning the litters were reduced to 2/sex/dose from each of 5 litters (20 pups/dose/strain) and maintained on test diets for 30 more days (Day 51) prior to sacrifice. There were only 9 pairs of CD strain rats at the 5% diet level. Remaining animals were necropsied within a few days post weaning. At termination offspring were grossly examined and necropsied. Parental and F1 generation animals were observed 2x/day for clinical signs. Body weight gain and standard reproductive indices were assessed and statistically compared using ANOVA and Dunnett's-t-test using SAS statistical programs. Parameters evaluated consisted of: fertility index, number of offspring born per dam; number and proportion of each sex born; number (Day 0, 1, and 21) and proportion (Day 1 and 21) of each sex alive; average weight at Day 1 and 21 of all offspring and of each sex.

Remark : Other studies have demonstrated an increased incidence of renal and bladder calculi formation in weanling animals when compared to adults consuming the same dietary level of TPA. This apparent increased sensitivity can be explained by the large amount of feed consumed in relation to body weight for young animals experiencing their initial growth spurt. Weanling animals are not more sensitive to TPA when the results are expressed on a mg/kg basis.

Conclusion : The NOAEL for reproductive toxicity was >5% in the diet (approximately 2480-3018 mg/kg/day). Whereas, the NOAEL for parental toxicity and the F1 generation was 0.5% TPA acid in the diet (approximately 240-307 mg/kg/day).

Reliability : (1) reliable without restriction

Reference : CIIT (1982) A Ninety-Day Study of Terephthalic Acid (CAS No. 100-21-0) Induced Urolithiasis and Reproduction Performance in Wistar and CD Rats. CITI Docket 11622

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

A.

Species/strain:	Rat
Sex:	Female [X]; Male []; Male/Female []; No data []
Route of administration:	Inhalation
Duration of test:	Throughout gestation
Exposure period:	Unknown
Frequency of treatment:	Unknown
Doses:	1 mg/m^3
Control group:	Yes [X]; No []; No data[]; Concurrent no treatment [X]; Concurrent vehicle []; Historical []
NOEL Maternal Toxicity:	1 mg/m^3

	NOEL Teratogenicity:	1 mg/m^3
	Results:	No abnormal developmental effects and no pre- or post-implantation losses were noted.
	Method:	Inhalation - Thirty pregnant rats were exposed to 1 mg/m^3 of DMT throughout gestation.
	GLP:	Yes []; No [X]; ? []
	Test Substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Krotov, Y.A. and Chebotar, N.A., 1972.
B.	**Species/strain:**	Rat/Wistar
	Sex:	Female [X]; Male []; Male/Female []; No data []
	Route of administration:	Oral gavage
	Exposure period:	Gestation days 7-16
	Frequency of treatment:	single daily exposure
	Doses:	1000 mg/kg
	Control group:	Yes [X]; No []; No data[]; Concurrent no treatment [X]; Concurrent vehicle []; Historical []
	NOEL Maternal Toxicity:	>1000 mg/kg
	NOEL Teratogenicity:	>1000 mg/kg
	Results:	No abnormal developmental effects and no pre- or post-implantation losses were noted. No maternal effects were noted.
	Method:	Unknown, anaimals were sacrificed on Day 21.
	GLP:	Yes []; No []; ? [X]
	Test Substance:	DMT
	Remarks:	The design, conduct, and data interpretation of this study cannot be evaluated due to the lack of the primary reference, and is limited by the lack of detail in the report.
	Reference:	Hoechst 1986
C.	**Species:**	Rat
	Sex:	Female
	Strain:	Sprague-Dawley
	Route of admin.:	Inhalation
	Exposure period:	days 6-15 of gestation
	Frequency of treatment:	6 hours/day for 10 consecutive days
	Duration of test:	20 days
	Doses:	1.0, 5.0, and 10.0 mg/m^3
	Control group:	yes; filtered room air
	NOAEL Maternal:	>10.0 mg/m^3
	NOAEL Fetal:	>10.0 mg/m^3
	Method:	Other
	Year:	1989

GLP:	Yes
Test substance:	as prescribed by 1.1-1.4
Remark:	Test material was supplied by the Amoco Corporation. Purity was not noted but typically exceeds 99%. Respirable time-weighted average concentrations were 0.90, 4.73, and 10.4 mg/m^3.
Result:	Maternal Effects: No mortalities occurred in any group. The incidences of clinical signs observed in rats exposed to TPA were similar to controls. No statistically significant differences were noted in mean dam body weight or weight gain, uterine weight, or implant number. Fetal Effects: No statistically significant differences were noted in mean litter weights, pup viability, or number of fetal malformations. External soft tissue examinations did not indicate any differences from control. However, internal examinations showed a slight increase in the incidence of rib anomalies in the middle dose (5.0 mg/m^3) group. This was only significant when all the various types of rib anomalies were added together.
Remark:	Rib anomalies were not deemed to be an indicator of teratogenesis because they were common variations, were not elevated in a dose-related manner, and occurred at a rate that was within the range of the laboratories own historical controls. Furthermore, no other signs of embryotoxicity were associated with this change.
Test condition:	Female rats weighing 117-150 g were quarantined and housed 2/cage with 1 male. Confirmation of mating was via evidence of sperm in a vaginal smear (Day 0), after which females were housed singly. The study consisted of 26-27 timed-pregnant dams per dose level. Exposures were by whole body inhalation conducted in 2 m^3 chambers with an airflow rate of 305-420 l/min. Test article was ground to respirable-sized particles using a Retsch Ultra-Centrifugal Mill. Chambers were sampled 2x/exposure period and TPA levels were determined by spectrophotometric analysis. Particle size was determined using a cascade impactor. Temperature, humidity and airflow were measured hourly. Animals were observed twice daily and given detailed physical exams daily on days 0 and 6-20. Dams were weighed on Days 0, 5 (randomization into groups), 6 (exposure initiation), 11, 16, and 20 (study termination). Standard "guideline" postmortem procedures were carried out on the females and their fetuses. Data were analyzed in an appropriate statistical manner using log transformations, multivariate ANOVA, single factor ANOVA and Dunnett's-"t"-test depending on the

nature and type of end-point assessed. The dam was considered to be a random factor and the pup a nested factor within the dam.

Reliability: reliable without restriction
Reference: Amoco Corporation (1989) and Ryan BM, et al. (1990).

5.10 OTHER RELEVENT INFORMATION

A. SPECIFIC TOXICITIES

Type: (neurotoxicity, immunotoxicity, etc.)
Results: No studies located
Remarks:
Reference:

B. TOXICODYNAMICS, TOXICOKINETICS

A - Species/strain: Rat
Method: Animals were fed diets containing 5% DMT for five-days
Results: DMT was reported to almost be completely absorbed and primarily eliminated by the kidney. Only a trace amount was found to be excreted unchanged in the urine; the rest is metabolized to terephthalic acid. About 15% of the unabsorbed ester appears in the feces; the balance is probably also destroyed by the intestinal flora.
GLP: Yes []; No [X]; ? []
Test Substance: DMT
Remarks: Interpretation of the study is limited by the lack of detail in the report.
Reference: Du Pont Co., Haskell Laboratory, unpublished data, MR-468-1, HL-55-58.

B - Species/strain: Rat/Charles River and Rabbit/New Zealand albino (used only for the studies using ocular administration)
Method: A 1% Triton-X-100 solution in water was used as a vehicle for the ocular, intratracheal, and dermal studies. The relative insolubility of DMT in the aqueous vehicle presented problems with dosing samples and storage of dosing solution. Probe sonification was used to suspend the DMT within the solution. Peanut oil was used as a vehicle in the oral studies.

Ocular administration - Eight albino rabbits were used to test the absorption and excretion of DMT

following ocular administration. A single 50 mg dose of C^{14}-labeled DMT (20 μCi/dose) was instilled into the conjunctival sac of one eye of each rabbit. Group I (5 animals) was exposed for five minutes after which the eyes were washed with copious amounts of distilled water and examined. Group II (3 animals) was exposed for 24-hours after which the eyes were washed with copious amounts of distilled water and examined. All rabbits were sacrificed 10-days after dosing.
Dermal administration - Doses were applied in 0.2 ml of vehicle to unabraded depilated dorsal skin of rats. The study used a single dose/day of 80 mg of C^{14}-DMT either for one-day (single dose) or for five doses over a 10-day period (one every other day). The same area of skin was used for dosing in the repeat dose dermal study and covered with a gauze patch in between dose administrations. In order to determine the total dose applied to the skin, the gauze patches were counted for residual radioactivity at the completion of the study.

Intratracheal administration - Parameters following intratracheal administration were measured using groups of five rats with either a single dose or five doses (one every other day) over a 10-day period. Dose levels were 0, trace (4 μCi), 5 mg, or 10 mg.

Oral administration - Parameters following oral exposure were measured using groups of five rats with either a single oral dose or five oral doses (one every other day) over a ten-day period. Oral dose levels were 0, trace (4 μCi), 20 mg, or 40 mg. Each dose contained 4 μCi tracer with or without added carrier compound.

Results:

Ocular administration - Approximately 29% of the C^{14}-label was recovered in the urine of rabbits receiving the five minute exposure and 37% of the dose was recovered following the 24-hour exposure. Fecal excretion was minimal. Examination of internal organs for C^{14}-label revealed only 0.1% remaining ten-days after the exposure.

Dermal administration - Approximately 11% of the C^{14}-label was recovered in the urine and feces in the 10-days following the single dermal exposure. Approximately 13% of the C^{14}-label were recovered in the urine and feces over the 10-day dosing period with the repeated dermal exposure. No evidence of

skin irritation occurred during the single or repeated dermal administrations.

Intratracheal administration - Total excretion (urine and feces) of a tracer dose of C^{14}-labeled DMT at the 24-hour time point after a single intratracheal administration was 53% of the total dose. Similar results (62%) were obtained at 48-hours. C^{14}-label in the urine was 52-58% of the total dose, and the feces contained 1.8-3.2% of the total dose. C^{14}-label remaining after repeated administration revealed less than 1% of the total dose remaining in the lungs and tracheal lymph nodes at 24-hours after the last administration. Negligible radioactivity (<0.1%) was found in all the other organs assayed. The largest percentage of the total radioactivity was recovered from the urine and smaller amounts in the feces after repeated dosing.

Oral administration - Greater than 83% of a single dose of C^{14}-labeled DMT was excreted within 48-hours post-dosing. The urine contained approximately 86% of the administered dose at 48-hours. Less than 10% of the radiolabel was in the feces at that time point. After dosing five times over a 10-day period, greater than 91% of the total administered dose was recovered from feces and urine within 24-hours of the final dose.

GLP: Yes []; No [X]; ? []

Test Substance: DMT - uniformly ring-labeled with Carbon-14 (obtained from Mallinckrodt Chemical Works, St. Louis, Missouri) and unlabeled DMT (Matheson Scientific Company, Cincinnati, Ohio)

Remarks: Overall, the data indicate that there is no significant bioaccumulation of DMT within the organism, even with repeated administration. Preliminary solvent extraction experiments with the feces and urine revealed a major portion of the radioactivity within the water-soluble fraction suggesting metabolism to more water soluble compounds.

Reference: Moffitt, A.E. Jr., *et al*. 1975.

C - Species/strain: Rat/F344 and Mouse/B6C3F1

Method: Male rats and mice received a single oral dose of C^{14}-DMT (ring-labeled). Urine and feces were collected over a 48-hour period for metabolite identification using reverse-phase HPLC.

Results: Urinary and fecal excretion accounted for 90% and 10% of the dose, respectively, in both species. Less

than 1% remained in the carcass after 48 hours. In the rat, terephthalic acid (TPA) was the only compound detected in the urine. While in mice, urinary metabolites consisted of monomethyl terephthalate (70%), TPA (30%) and traces of DMT. Similar metabolites were identified in the feces of both species. The possibility that DMT might lower the concentration of nonprotein sulfydryl groups also yielded negative results. Thus, demonstrating DMT is not activated to form electrophilic metabolites.

GLP: Yes []; No [X]; ? []
Test Substance: DMT (C^{14}-DMT; ring-labeled).
Remarks: None
Reference: Heck, H. d.'A., 1980.

D - Species/strain: Rat/F344
Method: Female rats (4/group) were fed diets containing 0, 1.0 or 2.0% DMT for three weeks. Fresh samples of urine were collected from each animal over the three-week exposure period. Urinary pH, electrolyte composition, and terephthalic acid concentrations were determined.
Results: Female F-344 rats fed diets containing 0, 1.0 or 2.0% DMT developed hypercalciuria and urinary acidosis. Metabolism of DMT to terephthalic acid (TPA) was demonstrated. The counter ion for urinary TPA appeared to be ammonium.
GLP: Yes []; No [X]; ? []
Test Substance: DMT
Remarks: None
Reference: Heck, H. d'A. and Kluwe, C.L., 1980.

C. OTHER

Risk Assessment Review:

Calcium terephthalate (Ca-TPA) is the major component of bladder stones induced by DMT in rats. Based on urinary solubility of Ca-TPA, normal human urine would become saturated with Ca-TPA at a TPA concentration of approximately 8 to 16 mM. Assuming that the average volume of urine excreted by man is 1.5 L/day and that DMT is metabolized entirely to TPA, the amount of DMT that would have to be absorbed to produce the minimum saturating concentration of TPA (8 mM) is 2,400 mg/day.
Remarks: A value of 2,400 mg/day is found in the reference. However, using a molecular weight of 194.2 x 8 mM x 1.5 L of urine per day I calculate the minimum daily dose to be 2,330 mg. This value is very conservative as it assumes 100% conversion of DMT to TPA and a similar quantitative excretion in the urine in one day.

Reference: Heck, H. d'A., and Tyl, R.W., 1985.

5.11 EXPERIENCE WITH HUMAN EXPOSURE

A.

Results: An oily paste containing 80% DMT showed no irritant effects 24-hours after 10 applications to human skin.

Remarks: Interpretation of this report is limited due to a sparseness of detail in the report and a lack of the primary reference.

Reference: Massmann, W., 1966.

B.

Results: A Russian study reports no adverse effects in workers exposed to high concentrations of DMT.

Remarks: Interpretation of this report is limited due to a sparseness of detail in the report and a lack of the primary reference.

Reference: Korbakova, A.I., 1964.

C.

Results: A Russian study reported moderate leukocytosis in workers involved in synthesis of DMT

Remarks: These workers were also exposed to other chemicals. Interpretation of this report is limited due to a sparseness of detail in the report and a lack of the primary reference.

Reference: Kamal'dinova, Z.M., *et al*., 1962.

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