FOREWORD INTRODUCTION

TRIMELLITIC ANHYDRIDE & TRIMELLITIC ACID

CAS N°: 552-30-7; 528-44-9

SIDS Initial Assessment Report
For
15th SIAM
(Boston, USA, 22-25 October 2002)

Chemical Name: Trimellitic Anhydride (TMA) and Trimellitic Acid (TMLA)

CAS No: 552-30-7, 528-44-9

Sponsor Country: U.S.A and ICCA

National SIDS Contact Point in Sponsor Country:

Mr. Oscar Hernandez
U.S. EPA
Risk Assessment Division (7403M)
1200 Pennsylvania Ave, NW
Washington, DC 20460
Tel: 202-564-7641
Hernandez.oscar@epa.gov

Industry: Mr. Dave Dutton
BP Amoco
150 W. Warrenville Road
Naperville, Illinois 60563
Tel: (630) 420-5079
duttondr@bp.com

HISTORY:

There was no additional testing needed to complete the SIDS endpoints. Collection of data and preparation of the documents was performed by industry with a separate review process from panel members. Documents were then submitted to the sponsor country. The sponsor country performed two independent reviews and prepared comments to industry for finalisation of documents to be considered at SIAM 14. Both industry and the sponsor country worked jointly to finalise documents for SIAM 14.

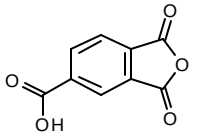
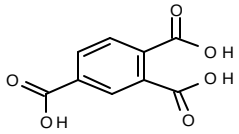
The follow data sources were reviewed in the preparation of this document: Hazardous Substance Data Base (HSDB), ChemSystems, 2000, SRI 2000, SRC PhysProp Database, Registry of Toxic Effects of Chemical Substances (RTECS), IUCLID, International Chemical Safety Cards, NIOSH Summary, OSHA Health Guidelines, International Occupational Safety and Health Information Centre, NTP Chemical Repository, ACGIH TLV Documentation. Literature searches were conducted on Medline, Publine and Toxline.

COMMENTS:

Deadline for circulation: February 1, 2002

Date of Circulation:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	552-30-7 528-44-9
Chemical Name	Trimellitic Anhydride (TMA) Trimellitic Acid (TMLA)
Structural Formula	TMA: $C_9H_4O_5$  TMLA: $C_9H_6O_6$ 

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

Trimellitic anhydride (TMA) and trimellitic acid (TMLA) are considered to be structural analogues. In addition, in aqueous environments TMA is readily converted to TMLA. TMA rapidly forms TMLA under the conditions used to test its toxicity, the toxicities of TMA and TMLA are qualitatively believed to be the similar for systemic toxicity with these two chemicals being presented as analogues. The only difference being sensitization and potentially local effects/reactions at the initial point of contact (skin, eye, and respiratory irritation). The sensitization potential of TMA, may be directly attributed to the formation of haptens following a reaction with proteins. TMLA does not react with proteins to form haptens, and therefore does not share this mode of action for sensitization.

Human Health

TMA exhibits low acute toxicity by the oral, dermal, and inhalation routes. The oral LD_{50} has been reported to range from 2,030 to 3,340 mg/kg in male and female rats, with stomach lesions appearing as the most consistent lesion upon necropsy. In rats, the inhalation LC_{50} value was reported to exceed a concentration of 2,330 mg/m^3, with lung lesions appearing as the most consistent lesion upon necropsy. The LC_{50} for TMLA was reported to be >3,750 mg/m^3, with necropsy findings considered within normal limits. A dermal LD_{50} value of 5,600 mg/kg was reported for TMA. Because TMA rapidly converted to TMLA in the body, the acute toxicity of TMLA is expected to be similar to that of TMA. Both chemicals are considered to have mild skin and severe eye irritation potential. Studies on TMA suggest that these materials may also be respiratory sensory irritants. TMA but not TMLA should be considered a dermal sensitizer.

In repeated dose inhalation studies, the principal effects of TMA are on the immune system and the lung. In a 13-week inhalation repeat dose study, elevated antibody levels and lung foci were observed in rats following exposures to relatively low concentrations of TMA (0.002 – 0.054 mg/m^3), however a NOAEL was not identified. Elevated antibody levels, asthma, allergic rhinitis, and a late respiratory systemic syndrome (LRSS) are associated with occupational exposures to TMA in some workers. The toxicity of TMA following repeated oral exposures is low, based on NOAELs of approximately 500 mg/kg-day identified for both rats and dogs. In a 13 week inhalation study, immunological and pulmonary effects were not associated with repeated exposures to TMLA; the NOAEL was determined to be 300 µg/m^3 (the highest dose tested). *In vivo* genotoxicity data are not available however, three *in vitro* assays with TMA were negative. Although a reproductive toxicity test has not been conducted for TMA, histopathological changes to reproductive tissues have not been observed in rats following subchronic exposures, and it has been found to be neither teratogenic nor fetotoxic in developmental toxicity studies.

Environment

TMA has a melting point of 165ºC, a boiling point of 390ºC, a vapor pressure of 7.6 x 10^{-5} Pa @ 25ºC, and assuming no hydrolysis a log K_{ow} of 1.95 and a water solubility of 1,036 mg/L. TMLA has a melting point of 219ºC, an unknown boiling point, a vapor pressure of 3.8 x 10^{-6} Pa @ 25ºC, a log K_{ow} of 0.95 and a water solubility of 21,000 mg/L. The half-life of TMA and TMLA in air is estimated to be 13.4 and 6.6 days, respectively, due to direct reactions with photochemically generated hydroxyl radicals. In the presence of water, TMA rapidly hydrolyzes (within 10 minutes) to form TMLA. Based on both chemicals physical chemical properties, TMA and TMLA are likely to partition to the water compartments in the environment. Acute toxicity testing in fish, invertebrates, and algae indicate a very low order of toxicity with measured No-Observed-Effect-Concentrations (NOECs) of 896, 792 and 739 mg/L, respectively. TMA and TMLA are readily biodegraded under aerobic conditions in sewage sludge, and are expected to biodegrade in soil and water as well. TMA and TMLA are not expected to bioaccumulate in food webs based on a BCF of 3.2.

Exposure

Approximately 100,000 metric tonnes/year TMA are produced worldwide, the majority of which (65,000 metric tonnes/year) are produced in the U.S. Most of the TMA produced (65%) is used in the synthesis of plasticizers for PVC resins, while smaller amounts (30%) are used as a reactant in wire and cable insulation enamels and polyester resins for powder coatings. When TMA is processed into the above materials, it is fully consumed and therefore, is not readily available for releases to the environment. All TMLA produced is used to make TMA. Occupational exposures to TMA and TMLA are likely to occur by the inhalation and dermal routes in settings where TMA is produced or used. Historical monitoring data have revealed mean concentrations ranging from 0.00051 to 0.77 mg/m^3. Because TMA is rapidly hydrolyzed to form TMLA in the presence of water, consumer and environmental exposures to TMA are not anticipated. Data regarding these potential exposures to TMLA are largely lacking, but exposures are expected to be low outside of the workplace.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Although a reproductive toxicity study and an *in vivo* genotoxicity are not available for TMA or TMLA, sufficient data are available to address these endpoints. Therefore, no additional studies are recommended to meet the SIDS data set.

Full SIDS Summary

CAS No.: 552-30-7		SPECIES	PROTOCOL	RESULTS
PHYSICAL CHEMISTRY				
2.1	Melting Point			165º C
				161-168º C
2.2	Boiling Point			390º C
				240-245º C @ 19 x 10^2 Pa
2.3	Density			1.54
2.4	Vapor Pressure		EPIWIN Suite, 1997	7.6 x 10^{-5} Pa
				1.3 x 10^{-3} Pa
				1.4 x 10^{-5} Pa
2.5	Partition Coefficient			After hydrolysis to TMLA
			KOWWIN v1.66	0.95
				No hydrolysis
			KOWWIN v1.66	1.95
			CLOGP	1.61
			ALOGP	0.80
			XLOGP	1.14
2.6	Water Solubility			After hydrolysis to TMLA
			Measured	21,000 mg/L
				Assuming no Hydrolysis occurs
			WSKOW V1.40	1,036 mg/L
			WSKOW v1.4	1,211 mg/L
			Int Act	860 mg/L
			AnalALOGSP	2,777 mg/L
	Hydrolysis		Measured	Hydrolysis complete within 10 minutes.
ENVIRONMENTAL FATE AND PATHWAYS				
3.1.1	Photodegradation		Estimate AOPWIN	Half-life: 13.4 days
3.2	Monitoring Data		Occupational	0.00051 – 0.77 mg/m^3
3.3	Environmental fate & distribution		Estimate v 2.2	Assumes hydrolysis to TMLA
			Level I	Air – 7.68 x 10^{-7}%
				Water – 99.2%
				Soil – 0.78%
				Sediment – 0.02%
			Level II	Air – 7.68 x 10^{-7}%
				Water – 99.2%
				Soil – 0.78%
				Sediment – 0.02%
			Level III	Air – 3.46 x 10^{-6}%
				Water – 50.6%
				Soil – 49.3%
				Sediment – 0.02%
3.5	Biodegradation		Modified Sturm (OECD 301B)	>60% within 7 days
				89-101% within 28 days
3.7	Bioaccumulation		Calculated BCFWIN v2.14	BCF = 3.2
ECOTOXICOLOGICAL DATA				
4.1	Acute Fish	*Leuciscus idus melanotus*	OECD 203	96-hour NOEC > 896 mg/L
4.2	Acute Daphnid	*Daphnia magna*	OECD 202	48-hour EC_0 > 792 mg/L
4.3	Acute Aquatic Plant	*Scenedesmus subspicatus*	OECD 201	96-hour NOEC > 739 mg/L
4.4	Toxicity to Bacteria	Activated sludge	OECD 209	EC_{50} - >100, <500 mg/L

CAS No.: 552-30-7		SPECIES	PROTOCOL	RESULTS
TOXICOLOGICAL DATA				
5.1.1	Acute Oral	Rat		LD_{50} = 2,730 mg/kg
5.1.2	Acute Inhalation	Rat Mouse		LC_{50} > 2,330 mg/m^3 LOEL = 21.5 mg/m^3
5.1.3	Acute Dermal	Rabbit Rat		LD50 > 2000 mg/kg LD50 = 5600 mg/kg
5.2.1	Skin Irritation	Rabbit		PDIS = 1.7/8
5.2.2	Eye Irritation	Rabbit		Draize score – 110/110
5.3	Sensitization	Guinea Pig Guinea Pig Mouse Mouse Mouse Rat	Dermal Dermal Dermal Dermal Dermal Dermal	Positive (in acetone) Negative (applied neat) Positive (in acetone/olive oil) Positive (in acetone/olive oil) Positive (in acetone/olive oil) Positive (in acetone/olive oil)
5.4	Repeated Dose	Rat		13-week inhalation study with 0, 3, and 38 week recovery: Slight increase in lung weight and volume, slight pulmonary pneumonia. Pulmonary physiology parameters unaffected Antibody levels elevated in a dose-dependent manner. Minimal effects in the 3 and 38 week recovery group. LOEL = 0.002 mg/m^3
		Rat		2-week inhalation study with 0-12 day recovery: NOAEL >0.3 mg/m^3
		Rat		6.5-week inhalation study: Increased lung weight, and volume, external hemorrhagic foci, inflammatory cell infiltration, and bronchoalveolar pneumonia. Effects were more severe than in the 13-week study Antibody levels and lung foci were elevated in a dose-dependent manner. LOEL = 0.002 mg/m^3
		Rat		2-week inhalation study: Increased hemorrhagic foci of the lung, increased lung weight, and TMA specific antibodies were observed. Effects greater in males than females. Estrogen reduced foci in both males and females. Testosterone had no effect. LOEL = 0.5 mg/m^3
		Rat		2,6, or 10 day inhalation study: No effect after 2 days, minimal lung injury after 6 days marked after 10 days . LOEL = 0.1 mg/m^3
		Mouse		5-day inhalation study, 14-day recovery: Decreased time of inspiration and expiration, increased length of apneic periods. LOEL 0.01 mg/m^3
		Rat		1-2-week inhalation study, 0-12 day recovery: Antibody response elevated in a dose-dependent manner at ten and 22 days but not at five days. Lung foci completely resolved after 12 days of recovery, but reappeared following a single challenge exposure. LOEL = 0.01 mg/m^3
		Rat	Respiratory Sensitization	Animals exposed on day 1,5, and 10, challenged on day 22 or 29 inhalation study: Elevated antibodies

				correlated to the number of lung foci, lung weight and lung displacement volume. LOEL = 0.33 mg/m^3
		Rat		1-10 day inhalation study: Lung injury and antibody levels increased on day 7-10. LOEL0.5 mg/m^3
		Rat		2,6, or 10 day inhalation study: Increase antibody levels. LOEL 0.1 mg/m^3
		Rat		13-week oral feeding study: No effect on appearance, behavior, pathology, or urine values. Dose dependent increase in leukocyte count. LOEL = 1000 ppm in the diet or approximately 50 mg/kg
		Rat		90-day oral feeding study: No effects on appearance, behavior, pathology, urine values or leukocyte count. NOEL = 10,000 ppm in the diet or approximately 500 mg/kg.
		Dog		13-week oral feeding study: No effects observed on appearance, behavior, pathology, serum chemistry, or urine values. NOEL 20,000 ppm in the diet or approximately 500 mg/kg
5.5	Genetic Toxicity In Vitro			
A	Bacterial	*Salmonella typhimurium*	OECD 471	Negative with and without metabolic activation.
		Salmonella typhimurium	OECD 471	Negative with and without metabolic activation
B	Non-Bacterial	Chinese Hamster Ovary Cells	OECD 476 (HGPRT mutation assay)	Negative with and without metabolic activation
		Chinese Hamster Ovary Cells	OECD 473 (chromosome aberration)	Negative with and without metabolic activation
5.6	Genetic Toxicity In vivo			
5.7	Carcinogenicity			
5.8	Reproductive Toxicity		Repeat dose	No effect on reproductive organs in two rat and one dog sub-chronic feeding studies. NOEL approximately 500 mg/kg No effect of reproductive organs in sub-chronic rat inhalation study NOEL 0.054 mg/m^3
5.9	Developmental Toxicity/Terotogenicity	Rat, Guinea Pig	Developmental	No fetotoxicity or developmental toxicity at concentrations up to 0.5 mg/m^3. No maternal toxicity other than an increase in hemorrhagic lung foci. NOEL: for developmental and terotogenic effects 0.5 mg/m^3
5.10	Toxicokinetics	Rat		Tmax =<3 houurs. Elimination rate constanst ranged from 0.0015-0.214, biological half-life ranged from 3-46 days.

Full SIDS Summary

CAS No.: 528-44-9		SPECIES	PROTOCOL	RESULTS
PHYSICAL CHEMISTRY				
2.1	Melting Point		Estimate MPBPWIN v1.4	219º C
2.2	Boiling Point			Converts to anhydride prior to boiling
2.3	Density			
2.4	Vapor Pressure		EPIWIN MPBPWIN v1.4	3.8×10^{-6} Pa
2.5	Partition Coefficient		KOWWIN v1.66 CLOGP Int Anal Prog ALOGP XLOGP	0.95 0.57 0.81 0.78 0.87
2.6	Water Solubility			21,000 mg/L @ 25º C
ENVIRONMENTAL FATE AND PATHWAYS				
3.1.1	Photodegradation		Estimate AOPWIN	Half-life: 6.55 days
3.2	Monitoring Data			
3.3	Environmental fate & distribution		Estimate v2.2 Level I Level II Level III	 Air – 7.68×10^{-7}% Water – 99.2% Soil – 0.78% Sediment – 0.02% Air – 7.68×10^{-7}% Water – 99.2% Soil – 0.78% Sediment – 0.02% Air – 3.46×10^{-6}% Water – 50.6% Soil – 49.3% Sediment – 0.02%
3.5	Biodegradation		Modified Sturm (OECD 301B)	>60% within 7 days (test material TMA) 89-101% within 28 days (Test material TMA)
3.6	COD			
3.7	Bioaccumulation			
ECOTOXICOLOGICAL DATA				
4.1	Acute Fish	*Leuciscus idus melanotus*	OECD 203	96-hour NOEC > 896 mg/L (Test material TMA)
4.2	Acute Daphnid	*Daphnia magna*	OECD 202	48-hour EC_0 > 792 mg/L (Test material TMA)
4.3	Acute Aquatic Plant	*Scenedesmus subspicatus*	OECD 201	96-hour NOEC > 739 mg/L (Test material TMA)
4.4	Toxicity to Bacteria	Activated sludge	OECD 209	EC_5 - EC_{50} - >100, <500mg/L (Test material TMA)

CAS No.: 528-44-9		SPECIES	PROTOCOL	RESULTS
TOXICOLOGICAL DATA				
5.1.1	Acute Oral	Rat		LD_{50} = 2,730 mg/kg Test material TMA)
5.1.2	Acute Inhalation	Rat		LC_{50} > 3,750 mg/m^3
5.1.3	Acute Dermal	Rabbit Rat		LD50 > 2000 mg/kg (Test material TMA) LD50 = 5600 mg/kg (Test material TMA)
5.2.1	Skin Irritation	Rabbit		PDIS = 0.7/8
5.2.2	Eye Irritation	Rabbit		Draize score = 59.7/110
5.3	Sensitization	Rat	Inhalation	Negative
5.4	Repeated Dose	Rat Rat	Inhalation (OECD 407)	13-week inhalation study, NOEL: 0.3 mg/m^3 4-week oral gavage study: Abnormal findings were restricted to diarrhea at the highest dose. NOEL: 300 mg/kg
5.5	Genetic Toxicity In vitro			
A	Bacterial	*Salmonella typhimurium* *Salmonella typhimurium*	OECD 471 OECD 471	Negative with and without metabolic activation. (Test material TMA) Negative with and without metabolic activation (Test material TMA)
B	Non-Bacterial	Chinese Hamster Ovary Cells Chinese Hamster Ovary Cells	OECD 476 OECD 473	Negative with and without metabolic activation. (Test material TMA) Negative with and without metabolic activation. (Test material TMA)
5.6	Genetic Toxicity In vivo			
5.7	Carcinogenicity			
5.8	Reproductive Toxicity		Repeat dose	No effect on reproductive organs in two rat and one dog sub-chronic feeding studies. NOEL approximately 500 mg/kg No effect of reproductive organs in sub-chronic rat inhalation study NOEL 0.054 mg/m^3. (Test material TMA)
5.9	Developmental Toxicity/Teratogenicity			No fetotoxicity or developmental toxicity at concentrations up to 0.5 mg/m^3. No maternal toxicity other than an increase in hemorrhagic lung foci. NOEL: for developmental and terotogenic effects 0.5 mg/m^3. (Test material TMA)
5.10	Toxicokinetics	Rat		Tmax =<3 hours. Elimination rate constant ranged from 0.0015-0.214, biological half-life ranged from 3-46 days. (Test material TMA)

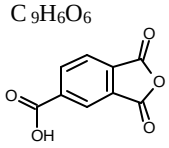
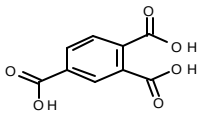
SIDS Initial Assessment Report

Analog Justification

Because TMA and TMLA are structurally similar, and because TMA is readily converted to TMLA in aqueous environments, information on these two chemicals is presented together in a single SIAP and SIAR. Studies on stability of TMA in water suggest complete hydrolysis occurs in less than ten minutes. Since TMA rapidly forms TMLA under the conditions used to test its toxicity, the toxicities of TMA and TMLA are believed to be the same with a few exceptions. Specifically, the allergic symptoms (both respiratory and dermal sensitization) of TMA are directly attributable to the reaction of TMA with free amines within proteins to form haptens, which when present at sufficiently high levels in tissues can produce sensitization. TMLA does not react with proteins to form haptens, and therefore does not share this mode of action for sensitization. In addition to the immunological differences, there may be some slight quantitative differences in reactions at the site of contact. While both materials cause slight irritation of the skin and are severe eye irritants, there appears to be a difference in the magnitude of response. This difference in the magnitude of irritation may be attributable to the heat of hydrolysis of the anhydride. With the exception of the immunological and site of contact effects, all other endpoints are expected to be the same.

1.0 IDENTITY

In the presence of water, trimellitic anhydride (TMA: CASRN 552-30-7) is readily and completely converted to trimellitic acid (TMLA: CASRN 528-44-9). The chemical properties of TMA and TMLA are summarized in the table below.

Property	Value
Chemical Formula	TMA: $C_9H_4O_5$ TMLA: $C_9H_6O_6$  TMA  TMLA
Molecular Weight	TMA: 192.12 TMLA: 210.14
Purity	TMA: 98% TMLA: >98%
Impurities	TMA: TMLA TMLA: --
Physical form:	TMA: Solid white flake TMLA: Solid white crystal
Melting Point	TMA: 165 °C TMLA: 219 °C
Boiling Point	TMA: 390 °C TMLA: --
Density	TMA: 1.54 g/mL at 20 °C TMLA: --
Vapor Pressure	TMA: 7.6×10^{-5} Pa at 25 °C TMLA: 3.8×10^{-6} Pa at 25 °C
Partition Coefficient (Log K_{ow})*	TMA: 1.95 (assumes no hydrolysis or reaction with the alcohol) TMLA: 0.95 (non-ionized form)
Water Solubility*	TMA: 1,036 mg/L (assumes no hydrolysis) TMLA: 21,000 mg/L
Hydrolysis Rate	TMA: Complete hydrolyse within 10 minutes.
Odor Threshold	--
Synonyms	TMA: 1,2,4-benzenetricarboxylic acid, cyclic 1,2-

	anhydride anhydrotrimellitic acid trimellitic acid anhydride 1,2,4-benzenetricarboxylic acid anhydride 1,3-dioxo-5-phthalancarboxylic acid 4-carboxyphthalic anhydride TMLA: 1,2,4-benzenetricarboxylic acid

*The water solubility and partition coefficient for trimellitic anhydride are listed above for completeness. However, the most environmentally relevant value must reflect hydrolysis of the anhydride to the acid.

2.0 GENERAL INFORMATION ON EXPOSURE

Manufacturing and Processing

In the U.S. trimellitic anhydride (TMA) is produced in a batch process. Pseudocumene and air, the raw materials, are mixed with solvent and catalyst in an enclosed reactor. The reaction is run to completion and to produce trimellitic acid (TMLA). TMLA, a reaction intermediate, is separated from the solvent and routed through a series of purification steps. It is then dehydrated to form trimellitic anhydride (TMA) and water as the byproduct. TMA is further treated to remove impurities, then flaked and stored in silos. TMA product is packaged for sale in bags of various sizes, most commonly, 1 and 0.5 metric ton, 50 Kg and 25 Kg. TMLA has no separate commercial value. Because the manufacturing system is a closed process, very little TMA is released to the environment during the production process. Solvent is recovered and recycled. Spent catalyst containing some impurities is routed to a catalyst recovery furnace. Catalyst is reclaimed. For the one and only manufacturing site in the U.S., waste streams are routed to an on-site wastewater treatment plant that utilizes both anaerobic and aerobic treatment processes.

Estimated National Production or Import Volume

Currently, TMA capacity worldwide is about 100,000 metric tonnes/year, which may be broken down to approximately 65,000 metric tonnes/year produced in the U.S. and the remainder produced outside the U.S (ChemSystems, 2000; SRI, 2000). In 1990, TMA production worldwide was estimated to be 50,000 metric tonnes/year (IPCS, 1992). Production in the 1970s was estimated to exceed 2.3 metric tonnes/year (HSDB, 2001). These data suggest that TMA production is generally increasing over time.

Uses and Functions

TMA is a highly reactive chemical and is a starting material for a variety of organic chemical products. Approximately 65% of the TMA produced in the U.S. is used in the synthesis of plasticizers for polyvinyl chloride (PVC) resins. These plasticizors have applications in wire and cable insulation, automotive parts and medical equipment. Approximately 30% of the TMA produced in the U.S. is used as a reactant in wire and cable insulation enamels and polyester resins in powder coatings. The remaining 5% of U.S. production is used for a variety of purposes including as an epoxy curing agent, textile sizing agent, rubber curing accelerator, electrostatic toner binder, and vinyl cross-link agent (ChemSystems, 2000; SRI, 2000). TMA is fully consumed in these uses and is therefore not available. 100% of the TMLA produced in the U.S. is used to make TMA.

Form of Marketed Product

TMA is used in the synthesis of plasticizers that are in turn compounded with PVC to make flexible plastic products such as automotive dashboards and coatings for electrical wire and cable. TMA is also used in polyester resin in products used in military, industrial and aerospace applications (ChemSystems, 2000; SRI, 2000). Many of the epoxy resin and surface coating systems may contain 2-10% reacted TMA within the polymer (OSHA, 1992). Coatings on the inside of tin cans used for foodstuffs contain up to 0.04% reacted TMA within the polymer.
No TMLA is marketed to consumers per se since all is used for the production of TMA.

2.1 Environmental Exposure and Fate

2.1.1 Photodegradation

Given their relatively low vapor pressures, TMA or TMLA that may be present in the atmosphere is expected to be associated predominantly with the particulate phase, which may be removed by both wet and dry deposition processes. Half-lives of 13.4 and 6.6 days have been estimated for TMA and TMLA, respectively, using the AOPWIN software (SRC, 2001) based on reaction with photochemically derived hydroxyl radicals.

2.1.2 Stability in Water

TMA is expected to rapidly hydrolyze to form TMLA in water (complete hydrolysis in 10 minutes in water at 27-32 °C) (Horan , 1962). Given their relatively low vapor pressures, volatilization of TMA or TMLA from surface water is also not expected to be significant. Based on studies using inoculated sewage sludge in which more than 50% of TMA/TMLA was degraded within 5 days (Letz *et al.*, 1987; Lebertz, 1991a), biodegradation of TMLA may occur in water under aerobic conditions.

2.1.3 Stability in Soil

TMA is expected to hydrolyze to form TMLA in moist soils. Given their relatively low vapor pressures, volatilization of either chemical from surface soils is not expected to be significant. Based on studies using inoculated sewage sludge in which more than 50% of TMA/TMLA was degraded within 5 days (Letz *et al.*, 1987; Lebertz, 1991), biodegradation of TMLA may occur in soils under aerobic conditions.

2.1.4 Environmental Transport and Distribution

Using default release estimates, predictions based on Levels 1 and 2 fugacity-based fate and transport models (Trent University, 1999) suggest that the majority of the TMA or TMLA released to the environmental will partition primarily to the water (99.2%) compartment, with a smaller amount found in the soil compartment (0.78%), and negligible amounts in the air and sediment (<0.1%) compartments. Although no specific information was located regarding the amount or mechanism of TMA release to the environment, a Level 3 fugacity model was also used. Based on a Level 3 fugacity model (Trent University, 1999), the majority (50.6%) of TMA/TMLA released is predicted to partition to the water compartment, with a slightly smaller amount in the soil compartment (49.3%), and negligible amounts in the sediment (<0.1%) and air (<0.1%) compartments. A larger percentage is predicted for soil by the Level 3 model, since this level allows for continuous release to soil. However, specific data regarding the direct release of TMA to soil were not located.

2.1.5 Biodegradation

TMA was readily degraded in screening tests using sewage sludge. Under aerobic conditions, 97% and 77% of the theoretical CO2 was generated within 28 days when TMA was tested at concentrations of 10mg/L and 20 mg/L respectively (Lebertz, 1991a). In another study 89-101% of the TMA was removed over a 4-week period (Letz et al. 1987). Given the rapid hydrolysis of TMA to TMLA in aqueous systems, results most likely reflect biodegradation of TMLA. TMA and TMLA are readily biodegradable under aerobic conditions in sewage sludge, are expected to biodegrade in water and soil as well and are not expected to bioaccumulate.

2.1.6 Bioaccumulation

Using v2.14 of BCFWIN a Bioconcentration Factor (BCF) of 3.2 was calculated for TMA and TMLA which suggests that they are not expected to bioconcentrate in aquatic organisms.

2.2 Human Exposure

2.2.1 Occupational Exposure

Occupational exposures to TMA or TMLA would most likely occur via the inhalation and dermal routes. Although little information is available to quantify potential dermal exposures, a number of studies have reported TMA concentrations in air associated with occupational exposures. It is assumed that workers are predominantly exposed to TMA. Average airborne TMA dust concentrations ranged from 0.006-2.1 mg/m^3 for production workers from three different job categories (Bernstein *et al.*, 1983). After engineering improvements were made, TMA concentrations decreased to approximately 0.01 mg/m^3. Industrial hygiene data from a TMA production plant in 1989 revealed exposure concentrations ranging from 0.003 to 0.77 mg/m^3 (Grammer *et al.*, 1991). In the U.S. at the production site, TMA concentrations were measured over a 14-year period and determined to range from <0.001-2.1 mg/m^3 (in air) for workers belonging to several different job categories (Grammer *et al.*, 1992). The highest arithmetic mean TMA concentration detected in a resin factory was reported to be 0.0193 mg/m^3 (van Tongeren *et al.*, 1995). Geometric mean exposure concentrations calculated from personal monitoring data ranged from <0.00053 to 0.17 mg/m^3 for various exposure classes of workers at a large manufacturing complex producing TMA (Zeiss *et al.*, 1992; Grammer *et al.*, 1999). Average concentrations of TMA for a full shift were reported to range from 0.0005 to 0.0193 mg/m^3 for four facilities using TMA (Barker *et al.*, 1998).

Monitoring data collected for a TMA-manufacturing plant during 1988-1999, reported mean 8-hour TWA concentrations ranging from 0.002 to 0.43 mg/m^3 and STEL concentrations ranging from 0.045 to 0.70 mg/m^3 for workers from four different job categories (BP Amoco personal communication, 2001).

Occupational exposure limits (OELs) for TMA are listed below for several countries.

Exposure Limit (Country)	(mg/m^3)	(ppm)
TWA (Australia)	0.04	0.005
TWA (Canada)	0.04	0.005
MAK (Czechoslovakia) dust	0.04	0.005
fumes	0.005	0.0006
MAK (Germany)	0.04	0.005
MAK (Netherlands)	0.04	0.005
OES (United Kingdom)	0.04	0.005
NIOSH REL (U.S.)	0.04	0.005
ACGIH TLV (U.S.)	0.04	0.005
STEL (Germany)	0.08	0.01

In 1978, NIOSH estimated that approximately 20,000 workers in the U.S. had potential for exposure to TMA in various applications and processes (OSHA, 1992).

2.2.2 Consumer Exposure

Because TMA rapidly hydrolyzes to form TMLA, consumer exposure to TMA is not expected to occur. TMA present in consumer products is generally reacted to form polymers and therefore is contained within the matrix of the polymer. As a result, potential exposures to consumers is negligible

2.2.3 Indirect Exposure via the Environment

Based on manufacturing and processing procedures in the U.S., releases to the environment are anticipated to be negligible. In addition, TMA rapidly hydrolyzes to form TMLA in the presence of water therefore, significant environmental exposures to TMA are not expected to occur.

Data regarding potential environmental exposures to TMLA were not located. As previously discussed, results from fugacity modeling indicates that should releases of the chemicals occur, the primary partitioning compartment would be the water.

3.0 HUMAN HEALTH HAZARDS

Analog Justification

Because TMA and TMLA are structurally similar, and because TMA is readily converted to TMLA in aqueous environments, information on these two chemicals is presented together in a single SIAP and SIAR. Since TMA rapidly forms TMLA under the conditions used to test its toxicity, the toxicities of TMA and TMLA are believed to be the same with perhaps two exceptions. Specifically, the allergic symptoms of TMA are directly attributable to the reaction of TMA with amino acids to form haptens, which when present at sufficiently high levels in tissues can produce sensitization. TMLA does not react with amino acids to form haptens, and therefore does not share this mode of action for sensitization. . In addition to the immunological differences, there may be some slight differences in reactions at the site of contact in terms of the magnitude of response. With the exception of the immunological and site of contact effects, all other endpoints are expected to be the same.

3.1. Toxicokinetics and Metabolism

Tissue concentration time-course data were collected for rats exposed to 0.95 mg/m^3 (TMA) for 45 minutes (IITRI, 1988a). Animals were sacrificed 3 hours, 1, 2, 4, 8, 16, and 32 days following exposure. In general, the highest tissue concentrations were obtained at the first time point (T_{max}<3 hours). A second T_{max} of eight days was reported for lung lymph nodes in male rats, suggesting a possible role in the gender differences observed for lung toxicity. Biological half-lives ranging from 3 to 46 days were estimated from the data (corresponding first order elimination constants of 0.015-0.214 /hour). Specific half-lives for TMA in the lungs were estimated to be 21 days in male rats and 16 days in female rats. Similarly, in lung associated lymph nodes, half-lives of 13 and 33 days were estimated for male and female rats, respectively. Because TMA is rapidly hydrolyzed to TMLA in the body, these data also likely reflect the kinetics of TMLA. Although one might anticipate that the half-lives of TMLA to be of shorter duration because unlike TMA, TMLA lacks the protein-reactive anhydride moity.

3.2 Acute Toxicity

Data available from laboratory animals exposed to TMA indicate that its acute toxicity is relatively low, regardless of the route of exposure.

- *Oral* – In rats, the acute oral LD_{50} value derived for female animals (2,030 mg/kg) was slightly lower than the value calculated for male animals (3,340 mg/kg) (IITRI, 1991a). For both sexes combined, an oral LD_{50} value of 2,730 mg/kg was derived. Upon necropsy of the animals that died, a number of stomach lesions (*e.g.*, wall thinning, ulcerations, hemorrhage, necrosis) were observed.
- *Inhalation* – In rats, 3/10 animals died following a four-hour exposure to 2,330 mg/m^3 TMA, indicating that the acute LC_{50} value is likely to exceed this concentration (IITRI, 1992a). No rats died following a four-hour exposure to concentrations as high as 3,750 mg/m^3 TMLA (IITRI, 1988b). Gross necropsy of the animals from the TMA study revealed a number of effects on the lung (*e.g.*, red foci, mottled, fluid-filled). Gross necropsy of the animals from the TMLA study revealed five rats with no gross lesions, three rats with lung foci, two with red areas on the lung and one with a distended bladder. The findings for the TMLA study were considered of a minor nature and within normal limits.

Altered breathing patterns (*e.g.*, decreased time of inspiration and expiration, increased length of apneic periods) were noted in mice exposed to 21.5-150 mg/m^3 for 30 minutes (Schaper and Brost, 1991).

- *Dermal* – In New Zealand albino rabbits, no deaths were observed following a dermal dose of 2,000 mg/kg (IITRI, 1991b). Dermal irritation was observed in all animals. However, no treatment-related lesions were noted upon necropsy. In rats, a dermal LD_{50} value of 5,600 mg/kg was reported (Rom, 1992).

Results of toxicities studies on TMA and TMLA suggest that the acute toxicity is relatively low independent of the route of exposure and that most effects noted were consistent with an irritation effect.

3.3 Irritation/Corrosiveness

3.3.1 Dermal

In rabbits, mild irritation (score=1.7/8.0) was observed following a 500 mg dermal dose of TMA applied to a 240 cm^2 patch of pre-moistened skin for 4 hours (IITRI, 1991c). Signs of irritation were generally resolved by the end of the observation period (14 days).

Dermal application of 500 mg TMLA produced irritation (0.7/8.0) in rabbits (IITRI, 1988d). The irritation was greatest during the first 60 minutes and was generally reversible by 48-72 hours. No signs of corrosivity were observed.

Results of studies suggest that both TMA and TMLA are slightly irritating to skin.

3.3.2 Eye

Similarly, ocular administration of TMA in rabbits produced signs of irritation reached a maximum (Draize score of 110.0/110.0) at 24-hours following exposure (Hatoum and Johnson, 1991).

Rabbits receiving an ocular dose of 100 mg TMLA reached a maximum eye irritation score of 59.7/110.0 at 24 hours. Lackluster pitting and pannus formation were observed.

Results of studies evaluating the potential of TMA and TMLA to cause eye irritation suggest that both materials should be considered severe eye irritants.

Results from skin and eye irritation studies imply that TMA may be slightly more irritating than TMLA. One possible explanation for this apparent difference in the magnitude of response may be the heat of hydrolysis of trimellitic anhydride. However, one should be cautious in deriving quantitative conclusions based on skin and eye irritations studies as these types studies tend to give qualitative rather than quantitative results.

3.4 Sensitization

- *Skin* - Although dermal exposure to a 30% solution of TMA in dimethyl sulfoxide (induction) and 5% TMA in acetone (challenge) (0.3 mL) produced dermal sensitization in guinea pigs (IITRI, 1987), dermal sensitization was not elicited in guinea pigs treated with 300 mg TMA powder (IITRI, 1993). In mice, dermal sensitization was elicited using 10-50% solutions of TMA in acetone/olive oil (0.025-0.050 mL) (Dearman *et al.*, 1992, 1996). In rats, dermal

sensitization was produced using 25-50% solutions of TMA in acetone/corn oil (0.15 mL) (Art *et al.*, 1998).

Dermal sensitization studies indicate that the presence of a solvent increases the dermal sensitization potential of TMA, perhaps by increasing absorption. While under normal conditions of manufacture and use TMA would be encounter as a powder and would not be used in a solvent it is prudent to consider TMA a potential dermal sensitizer. Studies on the potential dermal sensitization of TMLA were not available. However, TMLA is not likely a dermal sensitizer as it lacks the protein-reactive anhydride moity and furthermore TMLA was negative in respiratory sensitization potential studies.

- *Respiratory* - In a respiratory sensitization study rats were exposed to 50 ug/m^3 TMLA, six hours per day for five days (ITRI 1989b). Following a three-week rest period, animals were challenged with a single inhalation exposure to TMLA (50 ug/m^3), TMA (50 ug/m^3) or filtered air. There were no statistically significant effects on lung weight, volume, foci or serum IgG antibody levels. Results suggest that TMLA does not induce respiratory sensitization nor does it have cross-reactivity with TMA.

3.5 Repeated Dose

Data regarding the toxicity of TMA following repeated exposures are summarized below.

- *Oral* – No adverse effects have been observed in rats following dietary exposures to 1,000-10,000 ppm (50-500 mg/kg/day) TMA for 90 days (Hill Top, 1969; IBT, 1970). A dose-dependent increase in leukocyte count (NOEL 50 mg/kg/day) was observed in rats from one study (Hill Top, 1969), but was not observed in the second study (IBT, 1970). The eleveated leukocyte count reported in the Hill Top study may have been due to increased incidence of bronchitis, peribronchitis, and/or focal pneumonia reported in control and treated groups. Although a slight increase in adrenal weight was noted in dogs following dietary exposure to 1,000-20,000 ppm (25-500 mg/kg/day) TMA for 13 weeks, the number of animals tested per dose (two of each sex) was insufficient to assess the statistical significance of this increase. No adverse effects (histopathology) were observed in any treated animals.
- *Inhalation* – No adverse effects were observed in rats exposed to 0.3 mg/m^3 for six hours/day, five days/week for two weeks (IITRI, 1985). In rats exposed to 0.1 mg/m^3 TMA six hours/day, lung injury was absent after two days of exposure, minimal after six days of exposure, and marked after ten days of exposure (Zeiss *et al.*, 1988). A dose-dependent increase in antibody levels and lung foci was observed in rats exposed to TMA concentrations of 0.010, 0.030, 0.10 or 0.30 mg/m^3 for six hours/day, five days/week for one or two weeks (Zeiss *et al.*, 1987; Leach *et al.*, 1987). The lung foci completely resolved within 12 days after the last exposure, but reappeared following exposure to a single challenge concentration. Exposure to 0.5 mg/m^3 TMA produced hemorrhagic foci of the lung and increased antibody levels in rats treated for six hours/day, five days/week for two weeks (IITRI, 1992). Estrogen treatment reduced the number of lung foci in both male and female rats, while testosterone treatment had no effect. A dose-dependent increase in lung lesions (hemorrhagic foci, inflammatory cell infiltration, bronchoalveoloar pneumonia) and antibody levels was observed in rats exposed to 0.002, 0.015, or 0.054 mg/m^3 for six hours/day, five days/week for up to 13 weeks (Leach *et al.*, 1989). These effects were more pronounced in rats following 6.5 weeks of exposure than observed in animals following 13 weeks of exposure, suggesting some degree of adaptation. A NOEL was not identified. Mechanistic studies demonstrate that when the immune system of rats is suppressed, TMA exposure does not produce lung lesions (Leach et. al., 1989).
  In mice, exposure to 0.010, 0.070, or 0.150 mg/m^3 for 30 minutes/day for five days produced

altered breathing patterns (decreased time of inspiration and expiration, increased length of apneic periods) (Schaper and Brost, 1991). However, no histopathological changes were evident in the lungs of treated animals. Results are consistent with a sensory irritation effect. Data available from laboratory animals exposed to TMLA indicate that its subchronic toxicity is also relatively low, regardless of the route of exposure.

- *Oral* – Gastrointestinal symptoms (*e.g.*, diarrhea, watery cecal contents, cecal distortion) were apparent in rats exposed to 1,000 mg/kg-day TMLA by oral gavage five days/week for four weeks. However, no treatment-related effects were observed in rats exposed to TMLA doses of 300 mg/kg-day or less (Hankinson and Sakal, 1991).
- *Inhalation* – No treatment-related effects were observed in rats exposed to concentrations of 0.05, 0.1 or 0.3 mg/m^3 TMLA for six hours/day, five days/week for 13 weeks (IITRI, 1989a). In contrast to results obtained with TMA, exposure to TMLA failed to produce lung lesions or increased antibody levels in treated animals.

Repeat dose studies on TMA and TMLA suggest that the subchronic toxicity is relatively low regardless of the exposure route with the most notably effects being irritation at the site of application (TMA and TMLA) and an immunological response (TMA only).

3.6 Genetic Toxicity (In Vitro)

In vitro studies of the potential genotoxicity of TMA have consistently reported negative results. In Chinese hamster ovary cells, TMA concentrations as high as 2,000 mg/L failed to produce an increase in either HGPRT mutations or chromosomal aberrations in the presence and absence of a metabolic activation system (rat liver S9) (Bigger and Sigler, 1991; Putnam and Morris, 1991). Similarly, negative results were obtained for a mutagenic response in several strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) in the presence and absence of a metabolic activation system (rat liver S9) (San and Wagner, 1991). Because TMA is rapidly hydrolyzed to TMLA in aqueous solutions, these data likely reflect the genotoxicity of TMLA as well. Tests results suggest that the potential for genotoxicity is low for both TMA and TMLA.

3.7 Genetic Toxicity (In Vivo)

Although no *in vivo* genotoxicity studies were located for TMA or TMLA, the consistent negative results observed for these chemicals from *in vitro* studies suggests that the potential for significant genotoxicity is low.

3.8 Carcinogenicity

No data regarding the carcinogenicity of TMA or TMLA were located.

3.9 Reproductive Toxicity

Although a multigenerational reproductive toxicity test was not located for TMA or TMLA, data available from other studies suggest that the potential for significant toxicity to reproduction from exposures to these chemicals is low. For example, subchronic inhalation exposures of male and female rats to TMA concentrations up to 0.054 mg/m^3, or to TMLA concentrations up to 0.30 mg/m^3 did not result in any histopathological effects to reproductive tissues (IITRI, 1989a). Similarly, no

histopathological effects of reproductive tissues were observed in rats exposed to concentrations as high as 10,000 ppm TMA in feed (approximately 500 mg/kg-day) for 90 days (IBT, 1970; Hill Top, 1969), or in dogs exposed to concentrations as high as 20,000 ppm TMA in feed (approximately 500 mg/kg-day) for 13 weeks (Hill Top, 1969). Additionally, reproductive performance was not affected in female rats and guinea pigs following exposure to TMA concentrations of 0.5 mg/m^3 on days 6 through 15 of gestation (Ryan, 1988). Because TMA is likely hydrolyzed to form TMLA in tissues, these studies also provide information about TMLA. Data suggest a low potential for adverse reproductive effects.

3.10 Developmental Toxicity/Teratogenicity

Inhalation exposures to 0.5 mg/m^3 TMA for six hours/day on days 6-15 of gestation did not produce any signs of fetotoxicity or teratogenicity in guinea pigs (Ryan, 1988). In similarly treated pregnant rats, lung foci and increased antibody levels were observed (Ryan, 1988). Although no signs of fetotoxicity or teratogenicity were observed in the offspring, increased antibody levels were noted in neonatal rats. Following a challenge exposure, lung foci were only observed in the offspring whose mothers had not completely recovered from the original TMA exposure. Lung foci were not observed in adult offspring. With the exception of the effects on antibody levels and lung foci, these data likely reflect the toxicity of TMLA because TMA is rapidly hydrolyzed to TMLA in the body. Results are consistent with a low potential for developmental effects.

3.11 Human Experience

Eighteen workers were exposed to average concentrations of TMA ranging from 0.0006 to 2.1 mg/m^3 for three job categories (Bernstein *et al.*, 1983). Five of the workers were found to have elevated antibody levels to TMA, one worker had a late onset respiratory systemic syndrome (LRSS) associated with TMA, and another worker had allergic rhinitis. LRSS can be characterized by a series of immunological symptoms that are delayed, typically four to eight hours after exposure has ended and may include, coughing, wheezing, breathlessness, congestion, fever, chills, fatigue and generalized aching. Recovery is complete six to twelve hours after onset of symptoms.

An eleven-year study was conducted on 46 workers exposed to TMA. Seven workers had elevated antibody levels, one of which also had rhinitis and another of which had TMA asthma/rhinitis. Fourteen workers were found to have a positive antibody response to TMA-human serum albumen (TMA-HSA). Industrial hygiene data from a single year (1989) revealed concentrations ranging from <0.003 to 0.77 mg/m^3 (Grammer *et al.*, 1991, 1992).

A group of 119 workers who had the potential for exposure to TMA for at least one year were followed for a period of five years (Grammer *et al.*, 1998). Of the 16 workers with elevated levels of immunoglogin E (IgE), three had asthma, and an additional six developed asthma during the follow-up period. Of the 44 workers with elevated levels of immunoglobin G (IgG), six had asthma, and an additional two workers developed asthma during the follow-up period. Of the 102 workers without elevated IgE levels, none had asthma, and only a single worker developed asthma during the follow-up period. These data indicate that workers with elevated IgE or IgG levels are at increased risk of developing asthmatic allergic sensitivity to TMA.

In a group of 474 workers exposed to mean concentrations ranging from <0.00053-00.17 mg/m^3 TMA, 6.8% had a TMA immunologic syndrome, 31.6% had an irritant response, and 61.6% were asymptomatic (Zeiss *et al.*, 1992). An exposure-response relationship was apparent with increased antibody levels in this same group of workers when they were grouped into one of five exposure

groups (percent affected workers indicated in parentheses): 0.13 mg/m^3 (29%); 0.036 mg/m^3 (4%); 0.002 mg/m^3 (5%); 0.00051 mg/m^3 (0%); and <0.00053 mg/m^3 (0%) (Grammer *et al.*, 1999).

In a study of nine workers exposed to TMA-containing paint powder, one worker exhibited obvious illness and two worker had evidence of TMA-related pulmonary dysfunction and immunological response (Letz *et al.*, 1987). Monitoring data indicated that the workers had been exposed to concentrations of TMA in air that were more than 100-times higher than the occupation exposure limit of 0.04 mg/m^3.

A group of 196 workers were exposed to TMA over a 12-year period (Zeiss et al., 1990). Seventeen of the workers were found with IgE-mediated asthma/rhinitis, seven were found with LRSS, and four were found with both conditions.

Although all of the human exposures summarized above likely included some exposure to TMLA, no specific cases of human exposures to TMLA were located, and animal studies indicate that TMLA lacks the potential to sensitize and elicit an immune reaction.

4.0 HAZARDS TO THE ENVIRONMENT

4.1 Acute Aquatic Toxicity

Because TMA rapidly hydrolyzes to form TMLA in water, following pH adjustment TMLA and sodium trimellitate salts are the actual form of the chemical evaluated in aquatic toxicity tests. Analytical methods used measured the concentration of TMLA and its salt. Although information regarding the chronic toxicity of TMA/TMLA in aquatic species was not located, data regarding the acute toxicity of TMA/TMLA in aquatic species are summarized below.

- *Fish* – No signs of toxicity were observed in *Leuciscus idus melanotus* (Golden Orfe) exposed to TMA/TMLA nominal concentrations of 130, 220, 350, 600, or 1,000 mg/L for 96 hours under static conditions (Knacker *et al.*, 1993).Based on measured concentrations the 96 hour NOEC > 896 mg/l.
- *Invertebrates* - No signs of toxicity were observed in *Daphnia magna* (water flea) exposed to TMA/TMLA nominalconcentrations of 130, 220, 350, 600, or 1,000 mg/L for 48 hours under static conditions (Knacker *et al.*, 1992). Based on measured concentrations, the 96h NOEC was > 792 mg/l.
- *Plants* - No signs of toxicity were observed in *Scenedesmes subspicatus* (green algae) exposed to TMA/TMLA nominal concentrations of 62.5, 125, 250, 500, or 1,000 mg/L for 96 hours under static conditions (Knacker *et al.*, 1992). Based on measured concentrations, the NOEC was > 739 mg/l.
- *Bacteria* – In activated sludge, bacterial respiration was inhibited by TMA/TMLA (Lebertz, 1991). An EC_{50} value of 5.7 mg/L was calculated from the definitive portion of the respiration inhibition study. Preliminary tests in bacterial inhibition study tested 1, 10, and 100 mg/L and found minimal effects. The definitive portion of the study tested 500 to 4000 mg/L and found complete inhibition at all concentrations.

The calculated EC50 for respiration inhibition is not fully representative of the test results, that found 100 mg/L had minimal inhibition (approximately 6%) while 500 mg/L had nearly complete inhibition. The test report concluded that the EC50 must be in the range of between 100 and 500 mg/L. Consequently, the biodegradation test, conducted at 10 and 20 mg/L, would not be likely to reflect inhibitory effects of the test material.
Results suggest that TMA and TMLA have a low potential to cause significant acute aquatic toxicity.

4.2 Chronic Aquatic Toxicty

No data was available.

4.3 Terrestrial Effects

Although no data were located regarding the toxicity of TMA or TMLA in terrestrial mammals, the low toxicity in laboratory animals suggests that their toxicity to terrestrial mammals in general would also be low.

4.4 Other Environmental Effects

No additional data regarding other potential environmental effects of TMA or TMLA were located.

5.0 CONCLUSIONS AND RECOMMENDATIONS

TMA is currently of low priority for further work.

Approximately 100,000 metric tonnes/year TMA are currently produced world-wide, the majority of which (65,000 metric tonnes/year) are produced in the U.S. Most of the TMA produced (65%) is used in the synthesis of a plasticizer for PVC resins, while smaller amounts (30%) are used as a reactant in wire and cable insulation enamels and polyester resins in powder coatings. All of the TMLA produced in the world is used to produce TMA.

TMA exhibits low acute toxicity by the oral, dermal, and inhalation routes. The oral LD_{50} has been reported to range from 2,030 to 3,340 mg/kg in male and female rats (average = 2,730 mg/kg), with stomach lesions appearing as the most consistent lesion upon necropsy. In rats, the inhalation LC_{50} value was reported to exceed a concentration of 2,330 mg/m^3, with lung lesions appearing as the most consistent lesion upon necropsy. A dermal LD_{50} value of 5,600 mg/kg was reported. The inhalation LC_{50} for TMLA was reported to exceed 3,750 mg/m^3. For other routes, TMLA is expected to have similar or lower toxicity, based on the rapid hydrolysis of TMA to TMLA in tissues.

In repeated dose studies, the principle effects of TMA are on the immune system and the lung. Elevated antibody levels and lung foci have been observed in rats following subchronic exposures to relatively low concentrations (0.002 – 0.054 mg/m^3). Elevated antibody levels, asthma, allergic rhinitis, and LRSS are associated with occupational exposures to TMA in humans. However, humans appear to be less sensitive to these effects than are rats. The toxicity of TMA following repeated oral exposures appears to be low, with NOAELs of approximately 500 mg/kg-day identified for both rats and dogs. Immunological and pulmonary effects are not associated with repeated exposures to TMLA. Genotoxicity (*In vitro*) and developmental studies of TMA have generated negative results. Negative results for the genotoxicity and developmental toxicity of TMLA are inferred from the rapid hydrolysis of TMA to TMLA in tissues.

Based upon their chemical-physical properties, TMA and TMLA are not persistent in the environment and are not expected to bioaccumulate in food webs. In the presence of water, TMA rapidly hydrolyzes to form TMLA (complete hydrolysis in less than ten minutes). The half-life of TMA and TMLA in air is estimated to be 13.4 and 6.6 days, respectively, due to direct reactions with photochemically generated hydroxyl radicals. TMA and TMLA would be readily biodegraded under aerobic conditions. Biodegradation results likely reflect biodegradation of TMLA because of the rapid hydrolysis of TMA. Under environmentally relevant conditions TMLA is likely to be available as a salt. Human exposures to TMA and TMLA are likely to be limited to occupation settings where TMA is produced or used. Information regarding potential consumer or environmental exposure are generally lacking, but are expected to be low. Fugacity-based fate and transport modeling efforts suggest that TMA and TMLA are likely to partition to soil and water compartments in the environment. Acute toxicity testing in fish, invertebrates, and algae indicate a very low order of toxicity with no effect concentrations greater than 896, 792, and 739 mg/L respectively. The actual test material was likely trimellitic acid and it's sodium salt..

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SIDS DOSSIER: TRIMELLITIC ANHYDRIDE (TMA)
CAS No. 552-30-7

Sponsor Country: U.S.A.

DATE: January, 2002

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. **CAS-Number**: 552-30-7

B. **Name** *(IUPAC name)*: Trimellitic anhydride

C. **Name** *(OECD name)*: Trimellitic anhydride

D. **CAS Descriptor**

E. **EINECS-Number**: 209-008-0

F. **Molecular Formula**: C9H4O5

G. **Structural Formula**

H. **Substance Group**

I. **Substance Remark**

J. **Molecular Weight**: 192.12

1.02 OECD INFORMATION

A. **Sponsor Country:** U.S.A.

B. **Lead Organisation:**
Name of Lead Organisation: BP-Amoco Chemicals
Contact person: David Dutton
Address:

U.S.A.
Tel:
Fax:

1.1 GENERAL SUBSTANCE INFORMATION

A. **Type of Substance** element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

B. **Physical State** *(at 20°C and 1.013 hPa)*
gaseous [ ]; liquid [ ]; solid [X]

C. **Purity** *(indicate the percentage by weight/weight)*
98% purity, typical

1.2 **SYNONYMS**: 1,2,4-benzenetricarboxylic acid, cyclic 1,2-anhydride
anhydrotrimellitic acid
trimellitic acid anhydride
1,2,4-benzenetricarboxylic acid anhydride
1,3-dioxo-5-phthalancarboxylic acid

4-carboxyphthalic anhydride

1.3 IMPURITIES : trimellitic acid (TMLA)
methyl di-basic acids

1.4 ADDITIVES

1.5 QUANTITY

65,000 metric tonnes/year produced in U.S.
30,000 metric tonnes/year outside U.S.
Reference: SRI, 2000; ChemSystems, 2000

50,000 tonnes per annum in 1990
Reference IPCS, 1992
>2.27x106 g/year in the 1970s
Reference: HSDB, 2001

1.6 LABELLING AND CLASSIFICATION

Labelling
Type:
Specific limits:
Symbols:
Note:
R-phrases:
S-phrases:
Text of S-phrases:
Remarks:

Classification
Type:
Category of danger:
R-phrases:
Remarks:

1.7 USE PATTERN

A. General

65%: Synthesis of plasticizer in PVC resins
30%: Wire and cable insulation enamels and polyester resins in powder coatings
5%: Other – epoxy curing agent, textile sizing agent, rubber curing accelerator, electrostatic toner binder, vinyl cross-link agent

Type of Use:	**Category: Wide dispersive**
Industrial	Vinyl chloride plasticizers, Various polymers and polyesters, Dyes and pigments, Paints and coatings, Pharmaceuticals, Surface active agents, Specialty chemicals,

	Agricultural	Agricultural chemicals.
	Type of Use:	**Category: Non dispersive**
	Industrial	Curing agent for epoxy and other resins Numerous modifiers and intermediates

Remarks: A number of epoxy resin and surface coating systems, containing between 2-10% TMA, are available as dry powder formulations and are intended for application either by electrostatic dry powder spraying or by dipping pre-heated articles into fluidized beds
Reference: OSHA, 1992

B. Uses in Consumer Products

	Function	Amount Present	Physical State
Remarks:	Non-stick coatings on utensils and equipment in household and food industry	maximum of 10%	solid
Remarks:	Coatings (inside) of tin Cans for foodstuff	~0.04%	solid
Remarks:	Epoxy-resin based Surface coatings	10%	solid
Reference:	Amoco Corporation, 1991		

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Exposure limit value

Value: TWA 0.04 mg/m^3 (0.005 ppm)
Remarks: Australia
Reference: IPCS, 1992

Value: TWA 0.04 mg/m^3 (0.005 ppm)
Remarks: Canada
Reference: IPCS, 1992

Value: TWA 0.04 mg/m^3 (0.005 ppm) dust; 0.005 mg/m3 (0.0006 ppm) fumes
Remarks: Czechoslovakia (MAK)
Reference: IPCS, 1992

Value: TWA 0.04 mg/m^3 (0.005 ppm)
Remarks: Germany (MAK)
Reference: WHO, 1992

Value: TWA 0.04 mg/m^3 (0.005 ppm)
Remarks: Netherlands (MAK)
Reference: WHO, 1992

Value: TWA 0.04 mg/m^3 (0.005 ppm)
Remarks: United Kingdom (OES)
Reference: WHO, 1992

Value: TWA 0.04 mg/m^3 (0.005 ppm)
Remarks: U.S. (NIOSH REL, ACGIH TLV)
Reference: WHO, 1992

Short term exposure limit value
Value: 0.08 mg/m^3 (0.01 ppm)
Remarks: STEL - Germany
Reference: WHO, 1992

1.9 SOURCES OF EXPOSURE

(a)
Media of release: Airborne dust and fumes
Source:
Remarks: In 1978, NIOSH estimated that approximately 20,000 U.S. workers were at risk of exposure to trimellitic anhydride in its various applications. The NIOSH 1972 National Occupational Hazard Survey found 475 workers out of 3515 employed in nonmetallic mineral products and engine electrical equipment industries were exposed to TMA. The NIOSH 1982 survey found 97 workers of the total payroll of 269 in the printing ink industry were exposed to TMA.
Reference: OSHA, 1992

1.10 ADDITIONAL REMARKS

A. Options for disposal
Remarks:
Reference:

B. Other remarks

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

(a)
Value: 165°C (330°F)
Decomposition: Yes [ ] No [ ] Ambiguous [ ]
Sublimation: Yes [ ] No [ ] Ambiguous [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Amoco Corporation, 1997

(b)
Value: 161-168 °C
Decomposition: Yes [ ] No [ ] Ambiguous [ ]
Sublimation: Yes [ ] No [ ] Ambiguous [ ]
Method:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Amoco Corporation, 1991

2.2 BOILING POINT

(a)
Value: 390°C
Pressure:
Decomposition: Yes [ ] No [ ] Ambiguous [ ]
Method:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Amoco Corporation, 1991

(b)
Value: 240-245°C
Pressure: 19×10^2 Pa
Decomposition: Yes [ ] No [ ] Ambiguous [ ]
Method:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Amoco Corporation, 1991

2.3 DENSITY

(a)
Type: Bulk density [ ]; Density [X]; Relative Density [ ]
Value: 1.54
Temperature: 20°C
Method:
GLP: Yes [ ] No [ ] ? [X]
Remarks: specific density
Reference: WHO, 1992

2.4 VAPOUR PRESSURE

(a)
Value: 7.6 x 10^{-5} Pa, (5.69x 10^{-7} mmHg)
Temperature: 25°C
Method: calculated [X]; measured [ ] Year:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: US EPA, EPWIN Suite, 1997 (http://www.epa.gov/oppt/exposure/docs/episuitedi.htm).

(b)
Value: 9.86 x 10^{-6} mm Hg
Temperature: 25°C
Method: calculated [X]; measured [ ] Year:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Daubert, T. E., and R. P. Danner (1989)

(c)
Value: <1.1 x 10^{-7} mm Hg
Temperature: 25°C
Method: calculated [X]; measured [ ] Year:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Amoco Corporation, 1997

(d)
Value: 5.69 x 10^{-7} mm Hg
Temperature: 25°C
Method: calculated [X]; measured [ ] Year:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: MPBPWIN v1.40 in EPIWIN Suite

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

(a)
Log Pow: 0.95 – trimellitic acid (TMLA)
Temperature: room temperature
Method: calculated [X]; measured [ ]
GLP: Yes [ ] No [ ] ? [ ]
Remarks: TMA would have only transitory existence in an octanol/water mixture. Hydrolysis of TMA in aqueous alcohol is extremely rapid at room temperature. Consequently, TMLA would be formed upon dissolving TMA in this solvent system. Furthermore, small amounts of the diacid-octyl ester may form when octyl alcohol reacts with the anhydride moiety of TMA, though the hydrolysis reaction is more prevalent.
Test Substance TMA (hydrolysis to TMLA)
Reference: KOWWIN Version 1.66.

(b)
Log Pow: 1.95 (assumes no hydrolysis)
Temperature: 25° C
Method: calculated [X], measured [ ]

GLP:	Yes [], No [], ?[X]
Remarks:	If log Pow is estimated without considering hydrolysis of TMA to TMLA. Slightly larger estimates are obtained. However, the most environmentally relevant value must reflect the hydrolysis of the anhydride to the acid.
Test Substance:	Trimellitic anhydride
Reference:	KOWWIN (EPIWIN Suite)

(c)

Log Pow:	1.61 (assumes no hydrolysis)
Temperature:	25º C
Method:	calculated [X], measured [ ]
GLP:	Yes [ ], No [ ], ?[X]
Remarks:	If log Pow is estimated without considering hydrolysis of TMA to TMLA. Slightly larger estimates are obtained. However, the most environmentally relevant value must reflect the hydrolysis of the anhydride to the acid.
Test Substance:	Trimellitic anhydride
Reference:	CLOGP Program

(d)

Log Pow:	1.61 (assumes no hydrolysis)
Temperature:	25º C
Method:	calculated [X], measured [ ]
GLP:	Yes [ ], No [X], ?[ ]
Remarks:	If log Pow is estimated without considering hydrolysis of TMA to TMLA. Slightly larger estimates are obtained. However, the most environmentally relevant value must reflect the hydrolysis of the anhydride to the acid.
Test Substance:	Trimellitic anhydride
Reference:	Interactive Analysis Program

(e)

Log Pow:	0.80 (assumes no hydrolysis)
Temperature:	25º C
Method:	calculated [X], measured [ ]
GLP:	Yes [ ], No [X], ?[ ]
Remarks:	If log Pow is estimated without considering hydrolysis of TMA to TMLA. Slightly larger estimates are obtained. However, the most environmentally relevant value must reflect the hydrolysis of the anhydride to the acid.
Test Substance:	Trimellitic anhydride
Reference:	ALOG Program

(f)

Log Pow:	1.14 (assumes no hydrolysis)
Temperature:	25º C
Method:	calculated [X], measured [ ]
GLP:	Yes [ ], No [X], ?[ ]
Remarks:	If log Pow is estimated without considering hydrolysis of TMA to TMLA. Slightly larger estimates are obtained. However, the most environmentally relevant value must reflect the hydrolysis of the anhydride to the acid.
Test Substance:	Trimellitic anhydride
Reference:	XLOGP Program

2.6 WATER SOLUBILITY

A. Solubility

(a)
Value: 1,036 mg/L (assumes no hydrolysis)
Temperature:
Description: Miscible[ ]; Of very high solubility [ ];
Of high solubility [ ]; Soluble [X]; Slightly soluble [ ];
Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [ ]
Remarks: If water solubility estimated without considering hydrolysis to the acid, then lower values will be calculated.
Reference: SRC, 2001

(b)
Value: 21,000 mg/L (after hydrolysis to trimellitic acid)
Temperature 25° C
Description: Miscible [ ], Of very high solubility [ ], Of high solubility [ ], Soluble [X], Of low solubility [ ], Of very low solubility [ ], Not soluble [ ]
Method:
GLP: Yes [ ], No [ ], ? [ ]
Remarks: Upon contact with water, trimellitic anhydride rapidly hydrolyzes to trimellitic acid.
Reference SRC, 2001

(c)
Value: 1,211 mg/L (assumes no hydrolysis)
Temperature:
Description: Miscible[ ]; Of very high solubility [ ];
Of high solubility [ ]; Soluble [X]; Slightly soluble [ ];
Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [ ]
Remarks: If water solubility estimated without considering hydrolysis to the acid, then lower values will be calculated.
Reference: WSKOW v1.40 in EPWIN Suite

(d)
Value: 860 mg/L (assumes no hydrolysis)
Temperature:
Description: Miscible[ ]; Of very high solubility [ ];
Of high solubility [ ]; Soluble [X]; Slightly soluble [ ];
Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [ ]
Remarks: If water solubility estimated without considering hydrolysis to the acid, then lower values will be calculated.
Reference: Interactive Analysis Program

(e)
Value: 2777 mg/L (assumes no hydrolysis)
Temperature:
Description: Miscible[ ]; Of very high solubility [ ];
Of high solubility [ ]; Soluble [X]; Slightly soluble [ ];
Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [ ]
Remarks: If water solubility estimated without considering hydrolysis to the acid, then lower values will be calculated.

Reference: ALOGS Program

2.7 FLASH POINT *(liquids)*

(a)
Value: 227°C
Type of test: Closed cup [ ]; Open cup [x]; Other [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Amoco Corporation, 1991

2.8 AUTO FLAMMABILITY *(solid/gases)*

No data available

2.9 FLAMMABILITY

(a)
Results: Extremely flammable [ ]; Extremely flammable - liquefied gas [ ]; Highly Flammable [ ]; Flammable [ ]; Non flammable [ ]; Spontaneously flammable in air [ ]; Contact with water liberates highly flammable gases [ ]; Other [ ]
Method:
GLP: Yes [ ] No [ ] ? [ ]
Remarks: The National Fire Protection Association has not assigned a flammability rating to trimellitic anhydride. Other sources rate trimellitic anhydride as combustible when this substance is exposed to heat or open flame.
Reference: OSHA, 1996

2.10 EXPLOSIVE PROPERTIES

No data available

2.11 OXIDIZING PROPERTIES

No data available

2.12 ADDITIONAL REMARKS

Remarks: No additional remarks

2.13 ADDITIONAL DATA

No additional data

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

(a)

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Light source:	Sun light [ ]; Xenon lamp [ ]; Other [ ]
Light spectrum:	
Relative intensity:	
Concentration of Substance:	
Temperature:	
Direct photolysis:	
Half life:	13.4 days
Degradation:	
Quantum yield:	
Method:	calculated [X]; measured [ ] Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Trimellitic anhydride
Remarks:	Reaction rate with photo-chemically produced hydroxyl radicals estimated ($0.797x10^{-12}$ cm^3/mol-s)
Result:	Degrades on exposure to light or heat to high molecular weight addition products.
Reference:	AOPWIN (SRC, 2001); Horan, 1962; Amoco Corporation, 1991

3.1.2 STABILITY IN WATER

(a)

Type:	Aqueous hydrolysis
Half life:	
Degradation:	hydrolyzed within 10 minutes by stirring in water at 27-32ºC (80 to 90°F).
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Trimellitic anhydride
Remarks:	Degrades on exposure to light or heat to high molecular weight addition products.
Reference:	Horan, 1962; Amoco Corporation, 1991

3.1.3 STABILITY IN SOIL

No data available

3.2 MONITORING DATA (ENVIRONMENT)

No data available

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

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

No data available

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

(a)

Media: Air-biota [ ]; Air-biota-sediment-soil-water [X]; Soil-biota [ ]; Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]

Method: Fugacity level I [X]; Fugacity level II [X]; Fugacity level III [X]; Fugacity level IV [ ]; Other (calculation) [ ]; Other (measurement)[ ]

Results: Assumes no hydrolysis to the acid.

	Level I	**Level II**	**Level III**
Air	2.25E-4%	2.25E-6%	7.9E-4%
Water	92.5%	92.5%	36.5%
Soil	7.3%	7.3%	63.5%
Sediment	0.16%	0.16%	0.028%

Remarks: Estimates are based on the assumption that no hydrolysis occurs. Default release estimates assumed

Reference: Trent University, 1999

(b)

Media: Air-biota [ ]; Air-biota-sediment-soil-water [X]; Soil-biota [ ]; Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]

Method: Fugacity level I [X]; Fugacity level II [X]; Fugacity level III [X]; Fugacity level IV [ ]; Other (calculation) [ ]; Other (measurement)[ ]

Results: Estimated distribution and media concentrations reflecting trimellitic anhydride hydrolysis to trimellitic acid.

	Level I	**Level II**	**Level III**
Air	7.68E-7%	7.68E-7%	3.46E-6%
Water	99.2%	99.2%	50.6%
Soil	0.78%	0.78%	49.3%
Sediment	0.02%	0.02%	0.026%

Remarks: Trimellitic anhydride hydrolyses in water and under humid conditions to trimelltic acid (TMLA). Therefore, models using the physical chemical parameter for TMLA are thought to be more environmentally relevant.

Reference: Trent University, 1999

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Results:
Remarks:
Reference:

3.5 BIODEGRADATION

(a)

Type: aerobic [X]; anaerobic [ ]

Inoculum: adapted [ ]; non-adapted [ ]; ? [ ]; sewage [X]

Concentration: 10.19 mg/l related to COD [ ]; DOC [X]; Test substance [ ];

Medium: water [ ]; water-sediment [ ]; soil [ ]; sewage treatment [X]

Degradation:	>60% within 7 days
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; under test condition no biodegradation observed [ ], Other [ ]
Method:	OECD Guideline 301 B, Modified Sturm-Test
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic anhydride
Remarks:	Sewage microorganisms from a sewage plant working with predominantly domestic sewage used as the inoculum.
Reference:	Lebertz, 1991a

(b)

Type:	aerobic [X]; anaerobic [ ]
Inoculum:	adapted [ ]; non-adapted [ ]; ? [ ]; sewage [X]
Concentration:	100 ppm related to COD [ ]; DOC [ ]; Test substance [X];
Medium:	water [ ]; water-sediment [ ]; soil [ ]; sewage treatment [X]
Degradation:	89-101% over 4 weeks
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; under test condition no biodegradation observed [ ], Other [ ]
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Trimellitic anhydride
Remarks:	Since TMA rapidly hydrolyzes, this study assesses biodegradation of TMLA. This study was not considered key because full report was not available and specific protocol was not stated, though results were consistent with the key study (lebertz 1991a)
Reference:	Letz et al., 1987

3.6 BOD_5,COD OR RATIO BOD_5/COD

No data available

3.7 BIOACCUMULATION

Method:	Calculated
Type of test:	Bioconcentration Factor
GLP:	Yes [], No [X], ? []
Test substance:	Trimellitic anhydride
BCF:	3.2
Remarks:	
Reference:	BCFWIN v2.14

3.8 ADDITIONAL REMARKS

No additional remarks

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	static [x]; semi-static [ ]; flow-through [ ]; other [ ]; open-system [ ]; closed-system [ ]
Species:	*Leuciscus idus melanotus* (Golden orfe)
Exposure period:	96 hr.
Results:	LC_0 (96 hr): > 1000 mg/L LC_{50} (96 hr): could not be determined. NOEC (96 hr): = 1000 mg/L based on nominal concentrations NOEC (96 hr): >896 mg/L based on the measured average concentration of the highest concentration level tested.
Analytical monitoring:	Yes [x] No [ ] ? [ ]
Method:	OECD Guideline for Testing of Chemicals No. 203 "Fish, Acute Toxicity Test", adopted April 4, 1984 and the "German Water Endangerment Classification Scheme, DIN 38 412, Part 15" adopted June 1982.
GLP:	Yes [x] No [ ] ? [ ]
Test substance:	TMA hydrolyzes to TMLA in water. Test solutions were neutralized using sodium hydroxide. Therefore, the test material was trimellitic acid and its sodium salt.
Remarks:	The highest concentration causing no mortality within the period of the range-finding test was 1000 mg/L. The lowest concentration causing 100% mortality within the period of the range-finding test was >1000 mg/L
Reference:	Knacker *et al*., 1993.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

(a)

Type of test:	static [x]; semi-static [ ]; flow-through [ ]; other [ ]; open-system [ ]; closed-system [ ]
Species:	*Daphnia magna* (Straus)
Exposure period:	48 hr.
Results:	EC_0: >1000 mg/L EC_{50}: could not be determined. EC_0: >792 mg/L (based on the measured average concentration of the highest concentration level tested).
Analytical monitoring:	Yes [ ] No [ ] ? [ ]
Method:	OECD Guideline No. 202, Part I 'Daphnia sp., Acute Immobilisation Test and Reproduction Test" adopted April 4, 1984.
GLP:	Yes [x] No [ ] ? [ ]
Test substance:	TMA hydrolyzes to TMLA in water. Test solutions were neutralized using sodium hydroxide. Therefore, the test material was trimellitic acid and its sodium salt.
Remarks:	Highest concentration causing no immobilization within the period of the range-finding test: 100 mg/L. The lowest test concentration causing 100% immobilization within the period of the range-finding test: > 100 mg/L.
Reference:	Knacker, *et al.*, 1992.

4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

(a)

Species:	*Scenedesmus subspicatus* (green algae)
End-point:	Biomass [ ]; Growth rate [x]; Other [ ]
Exposure period:	96 hr.
Results:	NOEC = 1000 mg/L based on nominal concentrations; NOEC = 739 mg/L based on the measured average concentration of the highest concentration level tested.
Analytical monitoring:	Yes [x] No [ ] ? [ ]
Method:	OECD Guideline 201, 1984.
GLP:	Yes [x] No [ ] ? [ ]
Test substance:	It is thought that trimellitic anhydride was hydrolysed under test conditions. As a result it is believed that under test conditions and after pH adjustments to the required physiological value trimellitic acid and trimellitic sodium salt, respectively, were the test materials investigated in this study.
Remarks:	TMA hydrolyzes to TMLA in water. Test solutions were neutralized using sodium hydroxide. Therefore, the test material was trimellitic acid and its sodium salt.
Reference:	Knacker et al., 1993

4.4 TOXICITY TO BACTERIA

(a)

Type:	Aquatic [ ]; Field [ ]; Soil [ ]; Other [x]
Species:	activated sludge
Exposure Period:	3 hr.
Results:	The range-finding study tested 1, 10, 100 mg/L and found no or minimal inhibition (6% at 100 mg/L). The definitive portion of the study tested 500 to 4000 mg/L and found complete inhibition at all concentrations tested. The following EC values were extrapolated from data derived from the definitive portion of the study only: EC_5: 0.095 mg/L EC_{25}: 1.1 mg/L EC_{50}: 5.7 mg/L EC_{75}: 30.4 mg/L EC_{95}: 340 mg/L However, data obtained from the two studies combined suggest that the actual EC_{50} falls in the range between 100 and 500 mg/L.
Analytical monitoring:	Yes [ ] No [ ] ? [X]
Method:	OECD-Test Guideline 209 "Activated Sludge, Respiration Inhibition Test"
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic anhydride
Test Condition:	Activated sludge was added to the test solution and was aerated with compressed air for 3 hr. After the contact time, the solutions were poured into an oxygen-bottle and oxygen consumption was recorded for 10 minutes to determine respiration rates. TMA was likely hydrolyzed to TMLA under the conditions of this assay.
Reference:	Lebertz, 1991b

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

No data available, methods to extrapolate acute toxicity data to chronic exposures are readily available.

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

No data available

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data available

4.8 BIOTRANSFORMATION AND KINETICS

No data available

4.9 ADDITIONAL REMARKS

No additional remarks

5. TOXICITY

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/Sprague-Dawley
Value:	2,730 mg/kg
Method:	
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic anhydride administered 50% (w/v) suspension in corn oil
Remarks:	Groups of ten male and ten female rats were administered 0, 2000, 3500, or 5000 mg/kg TMA via gavage. Animals were observed for 14 days following exposure. A 95% confidence limit of 1,730-4,290 mg/kg was reported for both sexes combined, with slightly lower values reported for females (2,030 mg/kg: CL=700-5,890 mg/kg) than for males (3,340 mg/kg: CL=1,740-6,410 mg/kg). Deaths generally occurred within 1-48 hours after exposure. Stomach lesions (thinning, ulcerations, hemorrhage, necrosis) were noted.
Reference:	IITRI, 1991a

5.1.2 ACUTE INHALATION TOXICITY

(a)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [X]; Other [ ]
Species/strain:	Rat/Sprague-Dawley
Exposure time:	4 hours
Value:	2,330 mg/m^3
Method:	Particulate
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic anhydride - particle size = 4.4 microns (SD=2.3 microns)
Remarks:	Ten rats (five males; five females) were exposed to TMA for 4 hours. Three rats (two males; one female) died during the study. The acute inhalation LC_{50} value was therefore concluded to exceed 2,330 mg/m^3. During exposure rats exhibited labored breathing. Body weights were increased during the study. Gross necropsy revealed effects on the lung (red foci, mottled, fluid filled).
Reference:	IITRI, 1992a

(b)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [X]
Species/strain:	Mouse/Swiss-Webster
Exposure time:	30 min
Value:	LOEL = 21.5 mg/m^3
Method:	Aerosol dissolved in acetone
GLP:	Yes [] No [ ] ? [X]
Test substance:	Trimellitic anhydride - 21.5, 72, 150 mg/m^3, 75% particles < 0.65 um in diameter
Remarks:	Alterations in breathing patterns (decreased time of inspiration and expiration, increased length of apneic periods). No histopathological changes were evident. Authors concluded that respiration effects may be attributable to stimulation of vagal nerve endings in deep lung.
Reference:	Schaper and Brost, 1991

5.1.3 ACUTE DERMAL TOXICITY

(a)

Type:	LD_0 [X]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [ ]
Species/strain:	Rabbit/New Zealand albino
Value:	2000 mg/kg
Method:	Single dose applied to 240 cm^2 patch
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Undiluted trimellitic anhydride
Remarks:	Five male and five female rabbits received a single dermal dose of 2,000 mg/kg, applied for 24 hours. Animals were observed for 14 days following exposure. No deaths were observed. The authors concluded that the acute dermal LD_{50} value for TMA exceeds 2,000 mg/kg. Dermal irritation (erythema, edema) was observed in all animals immediately following the exposure, however, all animals recovered during the observation period. Body weights were slightly increased in females but unchanged in males. No treatment-related lesions were noted upon necropsy.
Reference:	IITRI, 1991b

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [X]
Species/strain:	Mice/female BALB/c
Value:	
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Undiluted trimellitic anhydride.
Remarks:	The ability of TMA and dinitrochlorobenzene to elicit immediate and delayed cutaneous hypersensitivity reactions in mice were compared. Topical exposure to both chemicals resulted in delayed hypersensitivity. Only TMA induced an immediate (1 hr) dermal reaction following local challenge. The study demonstrated that different classes of occupational chemical allergen exhibit a variable potential to elicit immediate and delayed dermal hypersensitivity reactions in mice, and provide a novel approach to the classification and characterization of human allergens.
Reference:	Dearman *et al.*, 1992.

(c)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	5,600 mg/kg
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	TMA
Remarks:	Study demonstrates a dermal LD50 of 5,600 mg/kg
Reference:	Rom, 1992.

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No data available

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

(a)

Species/strain:	Rabbit/New Zealand White

Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [X]; Not irritating [ ]
Classification: Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [X]; Not irritating [ ]
Method: 4-hours application of 0.5 g to a 240 cm^2 moistened skin patch
GLP: Yes [X] No [ ] ? [ ]
Test substance: Undiluted trimellitic anhydride
Remarks: Three male and three female rabbits were administered a single dermal TMA dose of 0.5 g to a 240 cm^2 patch of pre-moistened skin for four hours (excess chemical removed with light mineral oil). Animals were monitored for 14 days following exposure. A primary dermal irritation score of 1.7 (maximum of 8) was reported, however, effects generally reversed by the end of the observation period.
Reference: IITRI, 1991c

5.2.2 EYE IRRITATION/CORROSION

(a)
Species/strain: Rabbit
Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [x]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification: Irritating [x]; Not irritating [ ]; Risk of serious damage to eyes [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [x]
Test substance: Trimellitic anhydride
Remarks: Signs of ocular irritation were maximum (*i.e.*, Draize score = 110.0./110.0) at the 24-hour examination.
Reference: Hatoum and Johnson, 1991.

5.3 SENSITISATION

(a)
Type: Dermal Sensitization
Species/strain: Guinea Pig/Hartley
Results: Sensitizing [X]; Not sensitizing [ ]; ambiguous [ ]
Classification: Sensitizing [X]; Not sensitizing [ ]
Method:
GLP: Yes [ ] No [ ] ? [x]
Test substance: Trimellitic anhydride - 30% solution in dimethyl sulfoxide for induction; 5% solution in acetone for challenge.
Remarks: Ten adult male Hartley guinea pigs were administered 0.3 mL of the induction solution, once a week for three weeks. Two weeks after the last induction dose, the induced animals and ten control animals were administered 0.3 mL of the challenge solution once a week for two weeks. Positive erythema reactions were observed in 7/10 animals after the first challenge compared to 0/10 in controls; however, a majority of both treated and controls exhibited positive erythema reactions after the second challenge.
Reference: IITRI, 1987

(b)
Type: Dermal Sensitization
Species/strain: Guinea Pig/Hartley
Results: Sensitizing [ ]; Not sensitizing [X]; ambiguous [ ]

Classification: Sensitizing [ ]; Not sensitizing [X]
Method:
GLP: Yes [X] No [ ] ? []
Test substance: Undiluted trimellitic anhydride
Remarks: Ten adult male Hartley guinea pigs were administered 0.3 g TMA once a week for three weeks. Two weeks after the last induction dose, the induced animals and ten control animals were administered a 0.3 g challenge dose, and another challenge dose after an additional 13 days. Unlike the earlier study in which TMA was dissolved in dimethyl sulfoxide and acetone (see separate summary for IITRI, 1987), positive erythema reactions were not observed. The authors concluded that TMA was not sensitizing under the conditions of this study.
Reference: IITRI, 1993

(c)
Type: Dermal Sensitization
Species/strain: Mouse/BALB/c
Results: Sensitizing [X]; Not sensitizing [ ]; ambiguous [ ]
Classification: Sensitizing [X]; Not sensitizing [ ]
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: 10% trimellitic anhydride solution in acetone/olive oil (4:1)
Remarks: Groups of ten female mice received 50 µL of the test solution bilaterally on each shaved flank, followed by a second treatment after five days. Five days after the second treatment the mice had 25 uL of the test solution applied to the backs of both ears. Exposure produced an increase in hapten-specific immunoglobin E (IgE) and total IgE in serum. Cytokine secretion from lymph nodes cells displayed profiles characteristic of Th1 and Th2-type cell stimulation. Other chemicals were also tested in this assay.
Reference: Dearman *et al.*, 1996

(d)
Type: Dermal Sensitization
Species/strain: Mouse/BALB/c
Results: Sensitizing [X]; Not sensitizing [ ]; ambiguous [ ]
Classification: Sensitizing [X]; Not sensitizing [ ]
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: Trimellitic anhydride - 50% solution in acetone/olive oil (4:1)
Remarks: Groups of four female mice received 25 uL of the test solution on the backs of both ears. Three days following exposure the mice were injected with radiolabeled thymidine and sacrificed. Exposure to TMA produced an increase in serum IgE and a lymphocyte proliferation response. Other chemicals were also tested.
Reference: Dearman *et al.*, 1992

(e)
Type: Dermal Sensitization
Species/strain: Mouse/BALB/c
Results: Sensitizing [X]; Not sensitizing [ ]; ambiguous [ ]
Classification: Sensitizing [X]; Not sensitizing [ ]
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: Trimellitic anhydride - 10% solution in acetone/olive oil (4:1)
Remarks: Groups of ten female mice received 50 uL of the test solution bilaterally to each shaved flank once, followed by a repeat dose five days later.

Five days after the second treatment, animals received 25 uL of the test solution on the backs of both ears daily for three days. Exposure to TMA produced an increased expression of Th2 cytokines. Other chemicals were also tested.

Reference: Dearman *et al.*, 1996

(f)

Type: Dermal Sensitization
Species/strain: Rat/Norway and Wistar
Results: Sensitizing [X]; Not sensitizing [ ]; ambiguous [ ]
Classification: Sensitizing [X]; Not sensitizing [ ]
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: 50% - 25% TMA solutions in acetone/olive oil (4:1)
Remarks: Groups of six female rats received 150 uL of a 50% solution bilaterally to each shaved flank once. Seven days after the initial treatment, animals received 75 uL of a 25% solution on the backs of both ears. Two weeks following dermal exposure, animals were administered one or two challenge exposures to TMA via inhalation at concentrations ranging from 16-52 mg/m^3. Inhalation exposure to TMA produced dermal effects (encrustation, erythema, scaliness) to both flanks and ears within one day of exposure, persisting for two to five days. Serum IgE levels were elevated in Norway rats but not Wistar rats. However, both species responded to the respiratory challenge with altered breathing rates and histopathological changes to the larynx and lungs. Other chemicals were also tested.
Reference: Arts *et al*., 1998

5.4 REPEATED DOSE TOXICITY

(a)

Species/strain: Rat/Sprague-Dawley
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Inhalation
Exposure period: 6 hrs/day
Frequency of treatment: 5 d/wk; 13 wks
Post exposure observation period: up to 38 wks
Dose: 0, 2, 15, 54 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: --
LOEL: 2 ug/m^3
Method:
GLP: Yes [X] No [ ] ? [ ]
Test substance: Trimellitic anhydride
Remark: Three groups consisting of ten male and ten female Sprague Dawley rats each were exposed to TMA via inhalation for 13 weeks. Recovery times of 0, 3, and 38 weeks were evaluated. No treatment related deaths were observed. The lung appeared to be the only tissue affected, resulting in minimal treatment-related effects observed (slight increase in lung weight and volume and a small degree of pulmonary pneumonia). Pulmonary physiology parameters were unaffected. These results are in contrast to the more severe effects observed following 6.5 weeks of exposure under the same conditions (see separate summary), suggesting some degree of adaptation (immunologic tolerance). Antibody levels were elevated in a dose-dependent manner, beginning at the lowest dose tested. Lung foci were also increased in a dose-dependent manner,

beginning at the mid-dose in females and low-dose in males; however, statistical significance was achieved only in high-dose males due to large variability. Minimal effects were observed in the 3 and 38-week recovery groups.

Reference: Leach, 1989

(b)

Species/strain: Rat/Sprague-Dawley
Sex: Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration: Inhalation
Exposure period: 6 hrs/day
Frequency of treatment: 5 d/wk; 2 wks
Post exposure observation period: Up to 12 days
Dose: 0, 30, 300 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: 300 ug/m^3
LOEL: --
Method:
GLP: Yes [x] No [ ] ? [ ]
Test substance: TMA
Remark: Groups of 30 male Sprague Dawley rats were each exposed to 0, 30, or 300 mg/m^3 TMA via inhalation for two weeks. Recovery times of 0 and 12 days were evaluated. No deaths occurred during the study, no alteration in serum antibody levels, and no significant clinical signs were observed in the test article-treated groups. There were no statistically significant effects of treatment on body weights or body weight gains, organ weights, clinical chemistry or hematology parameters or serum antibody levels. There were no gross or histopathological lesions attributable to exposure to the test article. There were no effects seen on repeat (challenge) exposure to the test article.
Reference: IITRI, 1985

(c)

Species/strain: Rat/Sprague-Dawley
Sex: Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration: Inhalation
Exposure period: 6 hrs/day
Frequency of treatment: 5 d/wk; 6.5 wks
Post exposure observation period:
Dose: 0, 2, 15, 54 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: --
LOEL: 2 ug/m^3
Method:
GLP: Yes [X] No [ ] ? [ ]
Test substance: Trimellitic anhydride
Remark: Groups of ten male Sprague Dawley rats each were exposed to TMA via inhalation for 6.5 weeks. No treatment related deaths were observed. The lung appeared to be the only tissue affected, resulting in treatment-related effects (increased lung weight and volume, external hemorrhagic foci, inflammatory cell infiltration, and bronchoalveolar pneumonia) that were more severe than observed in similarly treated rats exposed for 13 weeks (see separate summary). Antibody levels and lung foci were elevated in a dose-dependent manner, beginning at the lowest dose tested.

Reference: Leach, 1989

(d)
Species/strain: Rat/Sprague-Dawley
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Inhalation
Exposure period: 6 hrs/day
Frequency of treatment: 5 d/wk; 2 wks
Post exposure observation period:
Dose: 0, 500 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: --
LOEL: 500 ug/m^3
Method:
GLP: Yes [X] No [ ] ? [ ]
Test substance: Trimellitic anhydride
Remark: Groups of ten male and ten female Sprague Dawley rats were exposed to 500 ug/m^3 TMA or filtered air via inhalation for two weeks. Group 1 animals received filtered air and served as controls. Groups 2 and 3 were gonadectomized. Group 3 animals were cross-treated with sex hormones (females given testosterone; males given estrogen). Group 4 served as the surgery control, and Group 5 only received TMA exposure. Changes in body weight were attributable to hormone exposure only. Hemorrhagic foci of the lung, increased lung weight, and TMA-specific IgG antibodies were observed in all animals treated with TMA. These effects were more pronounced in males than in females. Estrogen treatment reduced the number of foci in both males and females. Testosterone treatment did not have a significant effect. The precise mechanism by which estrogen alters TMA toxicity is not known, but suggests an interaction between the immune and endocrine systems.
Reference: IITRI, 1992

(e)
Species/strain: Rat/Sprague-Dawley
Sex: Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration: Inhalation
Exposure period: 6 hrs/day
Frequency of treatment: 2, 6, or 10 days
Post exposure observation period:
Dose: 0, 100 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: --
LOEL: 100 ug/m^3
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: Trimellitic anhydride (micronized powder)
Remark: Groups of 15 male Sprague Dawley rats were exposed to TMA via inhalation for two, six, or ten days. No effects were noted after two days of exposure. Exposure to TMA produced minimal lung injury and ultrastructural changes at six days, becoming marked at ten days. Similarly antibody levels in bronchoalveolar lavage (BAL) and serum were elevated in a duration-dependent manner at six and ten days. Antibody levels in BAL and serum were correlated with lung injury.
Reference: Zeiss *et al*., 1988; Pien *et al*., 1988

(f)

Species/strain:	Mouse/Swiss-Webster
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration:	Inhalation
Exposure period:	30 min/day
Frequency of treatment:	5 days
Post exposure observation period:	14 days
Dose:	0, 10, 70, 150 ug/m^3
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	--
LOEL:	10 ug/m^3
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Aerosol, dissolved in acetone
Remark:	Alterations in breathing patterns (decreased time of inspiration and expiration, increased length of apneic periods) were observed. No histopathological changes were evident. Authors concluded that respiration effects may be attributable to stimulation of vagal nerve endings in deep lung.
Reference:	Schaper and Brost, 1991

(g)

Species/strain:	Rat/Sprague-Dawley
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration:	Inhalation
Exposure period:	6 hrs/day
Frequency of treatment:	5 days/week, 1-2 weeks
Post exposure observation period:	0, 12 days
Dose:	0, 10, 30, 100, 300 ug/m^3
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	--
LOEL:	10 ug/m^3
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Trimellitic anhydride (micronized powder)
Remark:	Groups of 60 rats (40 male and 20 female) were exposed to TMA via inhalation for one or two weeks. Animals were sacrificed either after the last exposure or following a 12-day recovery period. Antibody response was elevated in a concentration-dependent manner beginning at the lowest concentration at ten and 22 days, but not at five days. A statistically significant correlation was reported for antibody levels and hemorrhagic lung foci after ten days. Lung foci completely resolved after 12 days of recovery, but reappeared following exposure to a single challenge concentration.
Reference:	Zeiss *et al.*, 1987; Leach *et al.*, 1987

(h)

Species/strain:	Rat/Sprague-Dawley
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration:	Inhalation
Exposure period:	6 hrs/day
Frequency of treatment:	days 1, 5, 10 (challenge on day 22 or 29)
Post exposure observation period:	1 day
Dose:	330, 500 ug/m^3
Control group:	Yes [ ]; No [X]; No data [ ];

Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL: --
LOEL: 330 ug/m^3
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: Trimellitic anhydride (micronized powder)
Remark: In the first study, six male rats were exposed to 500 ug/m^3 TMA for 6 hours/day on days one, five, and ten. Serum samples were collected every second day beginning on day 1 through 26. A six-hour challenge exposure of 540 ug/m^3 was administered on day 29 and animals were sacrificed on day 30. Serum antibody levels were increased beginning at day 5-7, reaching a peak one day that then declined for IgM, but plateaued for IgG. IgG levels were 10-fold higher than either IgA or IgM levels. In study 2, 18 male rats were exposed to 330 ug/m^3 TMA for 6 hours/day on days one, five, and ten. A six-hour challenge exposure of 300 ug/m^3 was administered on day 22 and animals were sacrificed on day 23. Antibody levels were highly correlated with the number of lung hemorrhagic foci, lung weights, and lung displacement volumes. In a third study, eight male rats were exposed to 500 ug/m^3 TMA for six hours/day on days one and 5. A six-hour challenge exposure of 500 ug/m^3 was administered on day 29 and animals were sacrificed on day 30. Again, antibody levels were highly correlated with the number of lung hemorrhagic foci, lung weights, and lung displacement volumes, even with only two exposures.
Reference: Zeiss *et al*., 1989

(i)
Species/strain: Rat/Sprague-Dawley
Sex: Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration: Inhalation
Exposure period: 4 hrs/day
Frequency of treatment: 1-10 days
Post exposure observation period: 1 day
Dose: 0, 500 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: --
LOEL: 500 ug/m^3
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: Trimellitic anhydride (micronized powder)
Remark: Groups of five male rats were exposed to 500 ug/m^3 TMA for four hours/day for one to ten days. Lung injury was markedly increased on days 7-10. Antibody response in serum and lung lavage fluid correlated with lung injury.
Reference: Zeiss *et al*., 1992

(j)
Species/strain: Rat/Sprague-Dawley
Sex: Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration: Inhalation
Exposure period: 6 hrs/day
Frequency of treatment: 2, 6, or 10 days
Post exposure observation period:
Dose: 0, 100 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]

NOEL: --
LOEL: 100 ug/m^3
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: Trimellitic anhydride (micronized powder)
Remark: Groups of ten male Sprague Dawley rats were exposed to TMA via inhalation for two, six, or ten days. Antibody levels were elevated in serum and bronchoalveolar lavage (BAL). Antibody levels in BAL were ~15 times higher than in matched serum pair.
Reference: Chandler *et al*., 1987

(k)
Species/strain: Rat/albino
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Diet
Exposure period: 13 weeks
Frequency of treatment: *ad libitum*
Post exposure observation period: none
Dose: 0, 1,000, 5,000, 10,000 ppm
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: --
LOEL: 1,000 ppm (assuming a food intake of 0.05 kg/kg-day, dose=50 mg/kg-day)
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: TMA
Remark: Groups of ten male and ten female rats were exposed to TMA in the diet for 13 weeks. No effects were observed with respect to appearance and behavior, pathology, or urine values. A dose-dependent increase in leukocyte counts was observed in both males and females. However, this effect was not observed in a second study conducted in rats (see summary for IBT, 1970).
Reference: Hill Top, 1969a

(l)
Species/strain: Rat/albino
Sex: Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration: diet
Exposure period: 90 days
Frequency of treatment: *ad libitum*
Post exposure observation period: none
Dose: 0, 10,000 ppm
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: 10,000 ppm (assuming a food intake of 0.05 kg/kg-day, dose=500 mg/kg-day)
LOEL: --
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: TMA
Remark: Groups of ten male and ten female rats were exposed to TMA in the diet for 90 days. No effects were observed with respect to appearance and behavior, pathology, or urine values. Unlike an earlier study conducted in rats (see summary for Hill Top, 1969) no treatment related effects were observed on leukocyte counts.
Reference: IBT. 1970

(m)

Species/strain:	Dog/beagle
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration:	Diet
Exposure period:	13 weeks
Frequency of treatment:	*ad libitum*
Post exposure observation period:	
Dose:	0, 1,000, 10,000, 20,000 ppm
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	20,000 ppm (assuming a food intake of 0.025 kg/kg-day, dose=500 mg/kg-day)
LOEL:	--
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	TTMA
Remark:	Groups of two male and two female dogs were exposed to TMA in the diet for 13 weeks. No treatment-related effects were observed with respect to appearance and behavior, pathology, serum chemistry, or urine values. Adrenal weights were slightly increased in treated animals, but could not be assessed statistically due to the small number of animals tested.
Reference:	Hill Top. 1969b

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL IN VITRO TEST

(a)

Type:	Mutagenicity			
System of testing:	*Salmonella* TA98, TA100, TA1535, TA1537			
Concentration:	33, 100, 333, 1000, 3333, 10000 ug/plate			
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]			
Results:				
Cytotoxicity conc:	1000			
Precipitation conc:	--			
Genotoxic effects:		+	?	--
	With metabolic activation:	[ ]	[ ]	[X]
	Without metabolic activation:	[ ]	[ ]	[X]
Method:	OECD 471			
GLP:	Yes [X] No [ ] ? [ ]			
Test substance:	TMA			
Remarks:	In the dose range-finding study, toxicity, but no precipitation, was reported at concentrations of 1,000 ug/plate or more. TMA did not produce a positive mutagenic response under the conditions of this assay.			
Reference:	San and Wagner, 1991			

(b)

Type:	Mutagenicity
System of testing:	*Salmonella* TA97, TA98, TA100, TA1535, TA1537
Concentration:	100; 333; 1,000; 3,333; 10,000 ug/plate
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:	
Cytotoxicity conc:	10,000 ug/plate
Precipitation conc:	--

Genotoxic effects: + ? --
With metabolic activation: [ ] [ ] [X]
Without metabolic activation: [ ] [ ] [X]
Method: Ames assay
GLP: Yes [ ] No [ ] ? [X]
Test substance: TMA
Remarks: TMA was not mutagenic under the conditions of this assay
Reference: Mortelmans *et al.*, 1986

B. NON-BACTERIAL IN VITRO TEST

(a)
Type: HGPRT mutations
System of testing: Chinese hamster ovary cells
Concentration: 500; 750; 1,000; 1,500; 2,000 ug/mL
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

Results:
Cytotoxicity conc: --
Precipitation conc: --
Genotoxic effects: + ? --
Without metabolic activation: [ ] [ ] [X]
Method:
GLP: Yes [X] No [ ] ? [ ]
Test substance: TMA dissolved in dimethylsulfoxide
Remarks: The mutagenicity of TMA was evaluated using the CHO/HGPRT assay with and without liver S-9 from Aroclor induced rats. Results were negative under the conditions of this assay.
Reference: Bigger and Sigler, 1991

(b)
Type: Chromosomal aberrations
System of testing: Chinese hamster ovary cells
Concentration: 260, 520, 1040, 2080 ug/mL
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

Results:
Cytotoxicity conc: Mitotic inhibition (41%) at highest concentration w/o activation
Precipitation conc: --
Genotoxic effects: + ? --
Without metabolic activation: [ ] [ ] [X]
Method:
GLP: Yes [X] No [ ] ? []
Test substance: TMA dissolved in dimethylsulfoxide
Remarks: The cytogenicity of TMA was evaluated using the CHO cells with and without liver S-9 from Aroclor induced rats. Toxicity, as indicated by mitotic inhibition, was noted at the highest concentration without activation. Results for chromosomal aberrations were negative under the conditions of this assay.
Reference: Putman and Morris, 1991

5.6 GENETIC TOXICITY IN VIVO

Although no in vivo genotoxicity studies were located for TMA or TMLA, the consistent negative results observed for these chemicals from in vitro studies suggests that the potential for significant genotoxicity is low.

5.7 CARCINOGENICITY

No data available

5.8 TOXICITY TO REPRODUCTION

Although a multigenerational reproductive toxicity test was not located for TMA or TMLA, data available from other studies suggest that the potential for significant toxicity to reproduction from exposures to these chemicals is low. For example, subchronic inhalation exposures of male and female rats to TMA concentrations up to 0.054 mg/m3, or to TMLA concentrations up to 0.30 mg/m3 did not result in any histopathological effects to reproductive tissues (IITRI, 1988, 1989). Similarly, no histopathological effects of reproductive tissues were observed in rats exposed to concentrations as high as 10,000 ppm TMA in feed (approximately 500 mg/kg-day) for 90 days (IBT, 1970; Hill Top, 1969), or in dogs exposed to concentrations as high as 20,000 ppm TMA in feed (approximately 500 mg/kg-day) for 13 weeks (Hill Top, 1969). Additionally, reproductive performance was not affected in female rats and guinea pigs following exposure to TMA concentrations of 0.5 mg/m3 on days 6 through 15 of gestation (Ryan, 1988). Because TMA is likely hydrolyzed to form TMLA in tissues, these studies also provide information about TMLA.

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a)

Species/strain:	Rat/Sprague-Dawley
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration:	Inhalation
Duration of the test:	6 hrs/day
Exposure period:	gestation day 6-15
Frequency of treatment:	Daily
Doses:	0, 500 ug/m^3
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL Maternal Toxicity:	--
NOEL Fetotoxicity:	--
NOEL Teratogenicity	500 ug/m^3
Results:	Lung foci and TMA-specific antibody were observed in exposed dams. TMA-specific antibody was also noted in neonatal rats. Lung foci were only observed in the challenged offspring whose mothers had not completely recovered from the original TMA exposure. Lung foci were not observed in adult rat offspring.
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	
Remarks:	No teratogenic effects or fetal deaths were observed.
Reference:	Ryan, 1988

(b)

Species/strain:	Guinea Pig/Hartley
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration:	Inhalation
Duration of the test:	6 hrs/day
Exposure period:	gd 6-15
Frequency of treatment:	Daily
Doses:	0, 500 ug/m^3
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]

NOEL Maternal Toxicity: --
NOEL Fetotoxicity: 500 ug/m^3
NOEL Teratogenicity 500 ug/m^3
Results: Lung foci and TMA-specific antibody were observed in exposed dams. TMA-specific antibody was also noted in serum of guinea pig fetuses, but not in neonatal guinea pigs. Unlike rats (see separate summary above), lung foci were not observed in neonatal or adult guinea pigs.
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance:
Remarks: No teratogenic effects or fetal deaths were observed.
Reference: Ryan, 1988

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

(a)
Type: Mechanistic study on lung foci in rats
Species/Strain Rat/Sprague-Dawley
Results: Mechanistic studies on the lung lesions of rats exposed to TMA via inhalation indicated that (1) if rats were immunosuppressed, then TMA did not cause lung lesions; (2) serum from nontolerant, TMA-sensitized rats contained antibody which when passively transferred into naïve recipient rats resulted in TMA-induced lung lesions following a single TMA challenge exposure; (3) enzyme, protein and cellular analyses of lung lavage fluid indicated that TMA produces pulmonary inflammation and resultant hemorrhage into the lung, but had no effect on macrophage function.
Remarks: The formation of lung lesions in rats following inhalation exposure to TMA was consistent with "immune complex injury" syndrome.
References: IITRI, 1988

(b)
Type: Mechanistic study on IgG binding
Species/Strain Human, Rat/Sprague-Dawley
Results: *In vitro* study of the inhibition of human and rat IgG binding by trimellitic rat serum albumin (TM-RSA) and trimellitic human serum albumin (TM-HSA). Rat IgG binding was inhibited by both TM-RSA and TM-HSA, while human IgG binding was inhibited only by TMA-HSA.
Remarks: Human IgG appears to be more specific than rat IgG.
References: Chandler *et al*., 1987

(c)
Type: Mechanistic study on inhalation exposure
Species/Strain Mouse/female BALB/c
Results: Atmospheres containing low molecular weight respiratory allergens can initiate specific IgE responses in mice and inhaled chemicals may differ in their ability to induce IgE antibody.
Remarks: Inhalation exposureto TMA resulted in the appearance of both serum IgG and IgE anti-hapten anitbody. Under the same exposure conditions, 2,4-dinitrochlorobenzene (a contact allergen that lacks the capacity for respiratory sensitization) failed to elicit detectable quantities of DNP antibody.
References: Dearman *et al.*, 1991.

(d)

Type:	Mechanistic study on IgE and IgG antibody responses to the trimellitic (TM) hapten group
Species/Strain	Mouse/ (BALB/c x A/J)F1 hybrids
Results:	The administration of TM-D-GL effectively abolished the ongoing IgE and IgG responses in mice previously immunized with TM-protein conjugate.
Remarks:	This study provides evidence for the potential clinical application of the D-GL immunotherapeutic approach to TM sensitivity.
References:	Liu *et al*., 1980.

(e)

Type:	Mechanistic study by inhalation
Species/Strain	Rat/Sprague-Dawley
Results:	Results confirmed that cyclophosphamide-treated rats showed very little if any blastogenic response to TMA. However, the saline-treated rats gave the normal immune response. Cyclophosphamide eliminated T- and B-cell function, which prevented the occurrence of TMA lesions.
Remarks:	Rats were exposed to 95 µg/m^3 TMA for six h/day, five days/wk for two weeks. The rats received daily injections of the immunosuppressant cyclophosphamide or saline.
References:	Leach *et al*., 1988.

(f)

Type:	Mechanistic study by dermal absorption
Species/Strain	Mouse/BALB/c strain, female
Results:	Mice were dermally exposed to TMA or to 2,4-dinitrochlorobenzene (DNCB) by repeated applications. An elevation in the expression of mRNA for interleukin 4 and interleukin 10 by lymph node cell from both the TMA and DNCB-treated mice was observed within six hours of culture and reaching maximum levels after 72 hours. Changes in cytokine mRNA in allergen-activated lymph node cells preceded protein production; however, the kinetic profiles were similar.
Remarks:	This study suggests that the divergent cytokine secretion profiles shown by mice treated by repeated dermal exposure to contact and respiratory allergens are primarily controlled at the level of transcription.
References:	Warbrick *et al.*, 1998.

B. Toxicodynamics, toxicokinetics

(a)

Type:	Distribution and Kinetic Study
Species/Strain	Rat/Sprague-Dawley
Results:	T_{max} = <3 hours Elimination rate constants ranged from 0.015 – 0.214 Biological half-lives ranged from 3-46 days
Remarks:	Fourteen male and 14 female Sprague-Dawley rats were exposed to 950 ug/m^3 ^{14}C-radiolabeled TMA (radiolabel was in the 2-carbonyl position) via whole body inhalation for 45 minutes. Particle sizing analysis was not performed because the test atmosphere was radioactive and therefore, the fraction of respirable particles was determined. Animals were sacrificed 3 hrs, 1, 2, 4, 8, 16, and 32 days post-exposure for tissue analysis. The highest concentrations were generally observed at the first time point (T_{max}<3 hours). A second T_{max} of eight-days was reported for lung lymph nodes in male rats, suggesting a potential role in gender lung toxicity in male rats as reported in a previous study. Sex differences in half-lives were reported for popliteal and lung lymph nodes, bone marrow, and heart.
References:	IITRI, 1988a

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(a)

Results: Highest arithmetic mean TMA exposures of 19.3 ug/m^3 were found in a resin factory (approximately half the eight-hour TWA OES of 40 ug/m^3).

Remarks: A retrospective cohort study was carried out in four factories (three alkyd resin factories and one cushioned flooring factory) to investigate the nature of exposure-response relationships for sensitization to TMA and other anhydrides. Arithmetic mean exposure levels to TMA were below their respective OES's in the resin factories. Relatively high full-shift exposures to TMA occurred in the cushioned floor facility, although no high peak exposures were detected.

Reference: van Tongeren *et al.* 1995

(b)

Results: Seven employees had positive IgE antibody levels against TM-human serum albumin, one of these employees had rhinitis, and another possibly had TMA asthma/rhinitis. Positive IgG antibody levels against TM-HAS was reported in fourteen employees (although only three had titers high enough to cause disease).

Remarks: This was an eleven year study of employees exposed to TMA that included periodic serum antibody studies and health questionnaires. Industrial hygiene data from the plant in 1989 reported exposures ranging from <0.003 mg/m^3 to 0.77 mg/m^3. Respirators with a protection factor of 100 were worn routinely in areas where TMA was used.

Reference: Grammer *et al.*, 1991.

(c)

Results: Personal monitoring data results included geometric means for different exposure classes: 1: 0.17 mg/m^3; 2: 0.087 mg/m^3; 3: <0.00055 mg/m^3; 4: <0.00041 mg/m^3; 5: <0.00053 mg/m^3. Nearly 7% of the employees had a TMA immunologic syndrome, 31.6% displayed an irritant response, and the remaining employees (61.6%) had no symptoms.

Remarks: Employees of a large chemical manufacturing complex were (n=474) studied to relate TMA exposure to serologic and clinical outcomes. All employees were assigned to a TMA exposure class from 1 (highest) to 5 (lowest).

Reference: Zeiss *et al*., 1992.

(d)

Results: Mean personal monitoring data results were presented by an exposure class: 1 (0.13 mg/m^3); 2 (0.036 mg/m^3); 3 (0.002 mg/m^3); 4 (0.00051 mg/m^3); and 5 (<0.00053 mg/m^3). Of the 28 employees that were assigned to exposure class 1, 29% developed disease (related to IgG or IgE titer). In exposure class 2, 4% of the employees developed disease, 5% of the employees in class 3 developed disease, and no employees developed disease in exposure classes 4 and 5.

Remarks: A three-year study of 286 employees of a TMA manufacturing facility was performed. Employees were assigned exposure classifications ranging from 1 (highest) to 5 (lowest), and immunological response was related to exposure.

Reference: Grammer *et al*., 1999

(e)

Results: Mean full-shift TMA exposure in four facilities ranged from 0.5-19.3 ug/m^{-3}

Remarks: Workers exposed to TMA were studied to determine the relation between exposure to TMA (and other acid anhydrides, AA) and the risk of developing skin prick test responses to AA-HSA.

Reference: Barker *et al.*, 1998.

(f)

Results: This study investigated nine workers who were exposed to a paint powder that contained TMA at a 55-gallon drum manufacturing plant. Environmental monitoring showed airborne TMA levels to be over 100 times the OHSA PEL of 0.04 mg/m^3.

Remarks: One employee exhibited obvious illness and two of the workers had definite evidence of TMA-related pulmonary dysfunction and immunologic response. Three workers showed IgG antibody against TM-HSA significantly higher than control serum. One worker showed IgE antibody against TM-HSA.

Reference: Letz *et al*., 1987

(g)

Results: Forty-six employees exposed to TMA were investigated using periodic serum antibody studies and questionnaires.

Remarks: Seven employees had positive IgE antibody against trimellityl-human serum albumin (TM-HSA), one had TMA rhinitis, and another potentially had TMA asthma/rhinitis. Positive IgG antibody against TM-HSA was observed in fourteen employees, although only three had titers high enouth to cause disease (none of them had symptoms associated with late respiratory systemic syndrome (LRSS) or pulmonary disease anemia (PDA)). TMA exposure concentrations for two different job categories ranged from <0.001-2.1 mg/m^3 and 0.005-0.32 mg/m^3 over a 14-year period.

Reference: Grammer, *et al.*, 1992

(h)

Results: Average airborne TMA dust concentrations ranged from 0.006 - 2.1 mg/m^3 for three different job categories. Five workers had antibody against TM-HSA, of these, three were diagnosed with the LRSS and one with TMA-induced allergic rhinitis. After local exhaust ventilation had been improved, average airborne dust concentrations decreased to approximately 0.01 mg/m^3 and the symptomatic improvement was noted in the individuals with the LRSS.

Remarks: Eighteen workers exposed to TMA powder were evaluated. Annual clinical evaluations and serum radioimmunoassays for total antibody binding and specific IgE binding to TM-HSA were performed.

Reference: Bernstein *et al.*, 1983

(i)

Results: A total of 119 subjects exposed to TMA for at least one year were identified from a previous cross-sectional study. These individuals were studied for the next five years to determine if they would develop an immunologic respiratory disease due to TMA exposure. In 1990, 16 individuals showed IgE against TMA conjugated to human serum albumin. Of these, three had immediate asthma and six developed asthma during the five-year follow-up. Of those without IgE against TM-HSA, none had immediate asthma in 1990 and only 1 out of 102 developed asthma after five years. Of those with IgG against TM-HSA (44), six had immunologic respiratory disease in 1990 and two more developed it in the following 5 years.

Remarks: Development of antibody (both IgE and IgG) against TM-HSA is predictive of subjects who have or will develop immunlogically mediated respiratory disease based on TMA exposure. The authors also concluded that the absence of antibody is a potent negative predictor.

Reference: Grammer *et al.*, 1998.

(j)

Results: Workers (n=196 individuals) involved in the manufacture of TMA were studied for 12 years. Seventeen workers had IgE-mediated asthma/rhinitis

with a positive prick test to TM-HSA (with IgE antibody of 0.8-57 ng TM-HSA bound/ml). Seven individuals had a late respiratory systemic syndrome (LRSS) and four workers had both syndromes. Three workers had late onset asthma, one had marked arthralgia and myalgia occurring hours after exposure to TMA.

Remarks: The authors reported a reduction in the number of workers exhibiting an immunologic syndrome during 1982-1987 in spite of the increased TMA production. This finding paralleled environmental control and worker education efforts.

Reference: Zeiss *et al.*, 1990.

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Robust Summaries for Trimellitic Anhydride

PHYSICAL/CHEMICAL ELEMENTS

MELTING POINT

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)

METHOD
- Method/guideline:
- GLP: ?
- Year (study performed):
- Remarks:

RESULTS
- Melting point: 165°C (330°F)
- Decomposition:
- Sublimation:
- Remarks:

CONCLUSIONS
- The melting point for TMA is 165°C

DATA QUALITY

REFERENCES
- Amoco Corporation. 1997. Material Safety Data Sheet (www.vetmed.ucdavis.edu/msds/mf/Amoco/files/01260000.html)

OTHER
- Values ranging from 161-168°C have been reported for TMA (Amoco Corporation, 1991).

BOILING POINT

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)

METHOD
- Method:
- GLP:
- Year (study performed):
- Remarks:

RESULTS
- Boiling point: 390°C (730°F)
- Pressure:
- Pressure unit:
- Decomposition (yes/no/ambiguous)
- Remarks:

CONCLUSIONS
- The boiling point for TMA is 390 °C

DATA QUALITY

REFERENCES
- Amoco Corporation. 1997. Material Safety Data Sheet (www.vetmed.ucdavis.edu/msds/mf/Amoco/files/01260000.html)

OTHER

VAPOR PRESSURE

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)
- Remarks:

METHOD
- Method: Calculated
- GLP:
- Year (study performed): 2002
- Remarks: Used SMILES notation of O=C(OC(=O)c1ccc(C(=O)O)c2)c12

RESULTS
- Vapor Pressure: 7.6×10^{-5} Pa (5.69×10^{-7} mm HG)
- Temperature: 25 °C
- Decomposition:
- Remarks:

CONCLUSIONS
- The vapor pressure for TMA is 7.6×10^{-5} Pa

DATA QUALITY
- Reliability: Klimisch Code 2 Reliable with restrictions, values is an estimate using an accepted method.

REFERENCES
- US EPA, EPIWIN Suite, 1997 (http://www.epa.gov/oppt/exposure/docs/episuitedl.htm).

OTHER
- Vapor Pressure: 9.86×10^{-6} mm Hg (Experimental), Daubert, T.E., and R.P. Danner (1989) (Data from MPBPWIN v1.40 database in EPIWIN Suite.)
- Vapor Pressure: 5.69×10^{-7} mm Hg (Calculated) (MPBPWIN v1.40 in EPIWIN Suite)
- Vapor Pressure: $<1.1 \times 10^{-7}$ mm Hg, Amoco Corporation. 1997. Material Safety Data Sheet (www.vetmed.ucdavis.edu/msds/mf/Amoco/files/01260000.html)

PARTITION COEFFICIENT

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)

METHOD
- Method: calculated
- GLP: No
- Year (study performed): 2002
- Remarks: Used SMILES notation of O=C(OC(=O)c1ccc(C(=O)O)c2)c12

RESULTS
- Log Pow: 0.95
- Temperature:
- Remarks: TMA would only have transitory existence in an octanol/water mixture. Hydrolysis of TMA in aqueous alcohol is extremely rapid at room temperature. Consequently, TMLA would be formed upon dissolving TMA in this solvent system. Furthermore, it is expected that small amounts of the diacid-octyl ester will form when octyl alcohol reacts with the anhydride moiety of TMA, though the hydrolysis reaction is more prevalent.

CONCLUSIONS
- The effective Log P_{ow} value for TMA is 0.95.

REMARKS
- The model predicts the Log Pow of the unionized form though it is expected that at least some of the trimeelitic acid would be ionized under environmentally relevant pH.

DATA QUALITY
- Reliability: Klimisch Code= 2 Reliable with restrictions. Value is an estimate using an accepted method.

REFERENCES
- KOWWIN Version 1.66. (http://www.epa.gov/oppt/exposure/docs/episuitedl.htm)

OTHER
- If Log P_{ow} is estimated without considering hydrolysis of TMA to TMLA, slightly larger estimates are obtained (see calculated values below). However, the most environmentally relevant value must reflect the hydrolysis of the anhydride to the acid. Consequently, the recommended value is the same as for TMLA.
- Estimated Log P_{ow}: 1.95 KOWWIN (EPIWIN Suite)
- Estimated Log P_{ow}: 1.61. CLOGP Program (http://www.daylight.com)
- Estimated Log P_{ow}: 1.61. Interactive Analysis Program (http://www.logp.com)
- Estimated Log P_{ow}: 0.80. ALOGP Program (http://www.lhn.unil.ch/Appl/cchem2.html)
- Estimated Log P_{ow}: 1.14. XLOGP Program (ftp2.ipc.pku.edu.cn)

WATER SOLUBILITY

TEST SUBSTANCE
- Identity: Trimellitic Anhydride (TMA)
- Remarks:

METHOD
- Method:
- GLP: ?
- Year (study performed):
- Remarks:

RESULTS
- Value: 21,000 mg/L
- Description of solubility:
- pH value and concentration at temperature °C:
- pKa value at 25 °C:
- Remarks: Moderate solubility after TMA hydrolysis to TMLA.

CONCLUSIONS
- TMA has moderate solubility in water after hydrolysis to TMLA. The recommended value is for TMLA.

DATA QUALITY

REFERENCES

- SRC PhysProp Database. 2001. (http://esc.syrres.com/interkow/webprop.exe) CAS=552-30-7.
- Amoco Corporation. 1997. Material Safety Data Sheet (www.vetmed.ucdavis.edu/msds/mf/Amoco/files/01260000.html)
- Trimellitic anhydride fact sheet, http://ull.chemistry.uakron.edu/erd/chemicals/2501-3000/2996.html

OTHER
- If water solubility is estimated without considering hydrolysis to acid, then lower values will be estimated, as in following:
- Water solubility: 1211 mg/L (Estimate reflecting melting point) (WSKOW v1.40 in EPIWIN Suite)
- Water solubility: 1036 mg/L. WSKOW v1.40 (in EPIWIN Suite)
- Water solubility: 860 mg/L. Interactive Analysis Program (http://ww.logp.com)
- Water solubility: 2777 mg/L. ALOGS Program, (http://www.lhn.unil.ch/Appl/cchem2.html)

ENVIRONMENTAL FATE ELEMENTS AND PATHWAYS

PHOTODEGRADATION

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)

METHOD
- Method/guideline: Estimated - AOPWIN
- Type (test type): Estimated
- GLP:
- Year (study performed): 2001
- The atmospheric hydroxyl radical concentration of 1.5×10^6 molecule/cm^3 was used as a standard default in the program.

RESULTS
- Direct photolysis:
- Half-life t ½ : 13.4 days (321.6 hours)
- Remarks: Overall OH Rate Constant: 0.80E-12 cm^3/molecule-sec. When exposed to humid air, TMA hydrolyzes to TMLA at an apparent linear rate. Because the estimated photolysis half-life of TMLA is shorter, the actual half-life of TMA in the air may be less than estimated.

CONCLUSIONS
- The direct photolysis half-life in air is estimated to be 322 hours. Actual half-life may be reduced if TMA hydrolyzes to TMLA in humid air.

DATA QUALITY

Reliability: Klimisch Code= 2 Reliable with restrictions. Value estimated using an accepted method.

REFERENCES
- SRC. 2001. Atmospheric Oxidation Program for Microsoft Windows (AOPWIN). Syracuse Research Center.

OTHER

STABILITY IN WATER

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)

METHOD
- Method/guideline: Aqueous hydrolysis
- Type (test type):
- GLP: No
- Year (study performed): 1962
- Remarks: 50 grams of TMA was added to 200 ml of distilled water at 80º F (27ºC). A temperature rise of 20 to 25 degrees was noted. Disappearance of trimellitic anhydride flakes took from 8 to 9 minutes. When flakes were dissolved the sample was filtered and an infra-red spectra was obtained. No absorption was noted at 5.35 or 5.60 microns, indicating complete hydrolysis of the anhydride,
- Duration: less than 20 minutes
- Positive Controls:
- Negative Controls:
- Analytical procedures: Infra-red spectrophotometry

RESULTS
- Measured value:
- Degradation: TMA hydrolyzed to form TMLA acid within 10 minutes by stirring with water at 80-90 ^{o}F (27-32ºC).
- Breakdown products: Trimellitic acid
- Remarks: While temperature was not held constant, the range was within environmentally relevant temperatures. The pH was not reported though one can assume the pH of distilled water to be between 6 and 7 depending on the amount of dissolved gas and upon addition of TMA the pH would drop to approximately 4.0.

CONCLUSIONS
- TMA was hydrolyzed to acid within 10 minutes in water at 80-90 ^{o}F.

DATA QUALITY
- Reliability: Klimisch Code= 2 Reliable with restrictions. Temperature and pH were not controlled.

REFERENCES
- Horan, 1962; Amoco Corporation, 1991.

OTHER

TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)
- Remarks:

METHOD
- Test (test type): Calculated
- Method: Levels I, II, and III
- Year (study performed): 2002
- Remarks: Half-lives in water, soil and sediment estimated using EPIWIN.
- Chemical Assumptions: Molecular weight – 192; water solubility – 21,000 g/m3; Vapor pressure – 7.6 x 10^{-5} Pa; Log P_{ow} – 0.95; Melting point – 165 ^{o}C; half-life in air – 321.8 hours; half-life in water – 360 hours; half life in soil – 360 hours; half-life in sediment – 1440 hours; all other parameters were default values. Level III model assumed continuous 1000 kg/hr releases to each compartment (air, water, and soil).

RESULTS
- Media: Air, soil, water and sediment concentrations were estimated.
- Estimated Distribution and Media Concentration reflecting TMA hydrolysis to TMLA:

	Level I	**Level II**	**Level III**
Air	7.7E-7%	7.6E-7%	3.4E-6%
Water	99.2%	99.2%	50.6%
Soil	0.78%	0.78%	49.3%
Sediment	0.02%	0.02%	0.02%

- Remarks: Since default assumptions for release estimates were used, resulting environmental concentrations are not provided.
- A biodegradation study showed that biodegradation of TMA/TMLA was more rapid than value used in this model: 65% biodegradation was reported within 5 days (i.e., $t_{1/2}$ in water <120 hours). Using a smaller value in the level III model reduces the concentration in water compartment (and reduces the percentage estimate).

CONCLUSIONS
- These results indicated that TMA, hydrolyzed to TMLA in water and under humid conditions, will partition primarily to water. Virtually no TMLA will partition to air. Soil and sediment concentrations will be minimal at equilibrium. The Level III model suggests soil may contain a significant percentage of TMLA, reflecting the assumed pattern of chemical release (equal loading of water, soil and air)..

DATA QUALITY
- Reliability: Klimisch Code= 2 Reliable with restrictions. Value is an estimate using an accepted method.

REFERENCES
- Trent University. 1999. Fugacity-based Environmental Equilibrium Partitioning Model. Version 2.2. Environmental Modeling Centre, Trent University, Peterborough, Ontario. (Available at http://www.trentu.ca/envmodel.)
- US EPA EPIWIN Suite. (Estimates of half-lives in water, soil, sediment from QSAR0

OTHER

- Using the EPIWIN software without modification to reflect hydrolysis of TMA to TMLA results in different estimates. For completeness, these are shown below. However, because of the relatively rapid and complete hydrolysis of TMA to TMLA in water or in humid conditions, the reasonably expected behavior of TMA will be that observed for TMLA
- Chemical Assumptions if TMA itself is modeled (i.e., ignoring hydrolysis): Molecular weight – 192; water solubility – 1211 g/m3; Vapor pressure – 7.6×10^{-5} Pa; Log P_{ow} – 1.95; Melting point – 165 ^{o}C; half-life in air – 321.8 hours; half-life in water – 360 hours; half-life in soil – 360 hours; half-life in sediment – 1440 hours; all other parameters were default values. Level III model assumed continuous 1000 kg/hr releases to each compartment (air, water and soil).
- Estimated Distribution and Media Concentrations if TMA itself is modeled:

	Level I	**Level II**	**Level III**
Air	2.25E-4%	2.25E-4%	7.9E-4%
Water	92.5%	92.5%	36.5%
Soil	7.3%	7.3%	63.5%
Sediment	0.16%	0.16%	0.028%

At equilibrium, TMA would partition to water, even un-hydrolyzed. However, the water solubility of TMA is estimated to be less than TMLA, so, under the constant loading of Model III, most of the TMA is found in the soil compartment.

BIODEGRADATION

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)
- Purity 98% with the majority of the remaining material being trimellitic acid.

METHOD
- Method/guideline: OECD 301B
- Test Type: Modified Sturm-Test
- GLP: Yes
- Year (study performed): 1991
- Contact time (units): 30 days
- Innoculum: sewage microorganisms
- Remarks field for Test Conditions: Two concentrations were tested: 10.19 and 20.29 mg/L TMA.

RESULTS
- Degradation % after time: For 10 mg/L TMA system, 97% of the theoretical CO_2 ($ThCO_2$) was generated within 28 days. For the 20 mg/L TMA system, 77% of the $ThCO_2$ was generated within 28 days
- For each time period %: For the 10 mg/L TMA system: Day 5 – 65% $ThCO_2$, Day 12 – 89% $ThCO_2$, Day 20 – 96% $ThCO_2$ and Day 30 – 99% $ThCO_2$.For the 20 mg/L TMA system: Day 5 – 57% $ThCO_2$, Day 12 – 72% $ThCO_2$, and Day 20 – 76% $ThCO_2$, Day 30 – 77% $ThCO_2$.
- Breakdown products: Carbon dioxide was measured.
- Remarks : TMA was degraded upon action of microorganisms under aerobic conditions. The biodegradation rates in the different concentrations were not the same rate. However, the criteria for "readily biodegradable" were achieved in both concentrations. Given the rapid hydrolysis of TMA to TMLA in aqueous systems, results most likely reflect biodegradation of TMLA.

CONCLUSIONS
- TMA is readily biodegradable.

DATA QUALITY
- Reliability: Klimisch Code= 1

REFERENCES
- Battelle Europe. 1991. Study on the Ready Biodegradability (modified Sturm Test) of Trimellitic Anhydride. Study-No: BE-EA-128-91-01-STT-01.

OTHER

ECOTOXICITY ELEMENTS

ACUTE TOXICITY TO FISH

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)
- Remarks: 98% pure

METHOD
- Method/guideline: OECD 203 and according to "German Water Endangerment Classification Scheme, DIN 38 412, Part 15".
- Type (test type): Acute toxicity to fish
- GLP: Yes
- Year (study performed): 1991
- Species/Strain/Supplier: *Leuciscus idus melanotus* (Golden orfe)
- Analytical monitoring: High performance thin-layer chromatography (HPTLC). The sample was treated with sodium hydroxide to hydrolyze the test substance completely. The alkaline solution was acidified with hydrochloric acid and evaporated to dryness under nitrogen. The residue was treated with diazomethane to form trimellitic acid trimethylester. The analyte was measured using HPTLC.
- Exposure period (unit): 96 hours
- Statistical methods: Probit Analysis
- Details of test: flow-through test system and static
- Remarks: TMA hydrolyzes to trimellitic acid (TMLA) in water. Test solutions were neutralized using sodium hydroxide. Therefore the test material was trimellitic acid and its sodium salt.

RESULTS
- Nominal concentrations: 130, 220, 350, 600, and 1,000 mg/L
- Measured concentrations: 70-129% (average of 95.8%)
- Element value: Based on nominal concentrations: LC_0=>1,000 mg/L; LC_{50}=could not be determined; NOEC=> = 1,000 mg/L. Based on measured average concentrations: NOEC = 896 mg/L.
- Statistical results: descriptive
- Remarks:

CONCLUSIONS
- TMA has low toxicity to *Leuciscus idus melanotus*.

DATA QUALITY
- Reliability: Klimisch Code= 1

REFERENCES
- Battelle Europe. 1993. A Study of the Acute Toxicity to Fish (*Leuciscus idus melanotus*) of Trimellitic Anhydride. Study Number: BE-EA-128-91-01-F3A-1.

OTHER

TOXICITY TO AQUATIC PLANTS (*e.g.*., ALGAE)

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)
- Remarks: 98% pure

METHOD
- Method/guideline: OECD 201
- Test type (static/other): static
- GLP: Yes
- Year (study performed): 1992
- Species/strain # and source: *Scenedesmus subspicatus* (Chodat, SAG 86.81); green algae.
- Element basis: THOMA Counting Chamber with Microscop Metalux II.
- Exposure period, date of start and end of the test [Duration]: 96 hours-
- Analytical monitoring: High performance thin-layer chromatography apparatus (HPTLC). The sample was treated with sodium hydroxide to hydrolyze the test substance completely. The alkaline solution was acidified with hydrochloric acid and evaporated to dryness under nitrogen. The residue was treated with diazomethane to form trimellitic acid trimethylester. The analyte was measured using HPTLC.
- Statistical methods: One-way Analysis of Variance (ANOVA) with Bonferroni multiple range test
- Remarks: Average initial cell density was 10^4 cells/mL; Temperature = 23 C; pH = 8.3. TMA hydrolyzes to trimellitic acid (TMLA) in water. Test solutions were neutralized using sodium hydroxide. Therefore the test material was trimellitic acid and its sodium salt.

RESULTS
- Nominal concentrations: 62.5, 125, 250, 500, and 1,000 mg/L
- Measured concentrations: 73-110% (average of 86.8%)
- Unit:
- Element value: After a 96 hour exposure, analysed concentrations of the test material were relatively unchanged from measurements at 0 hours.
- NOEC, LOEC, or NOEL, LOEL: Based on nominal concentrations: NOEC >=1,000 mg/L; Based on measured average concentrations: NOEC >= 739 mg/L.
- Was control response satisfactory: Yes
- Statistical results: descriptive.
- Remarks:

CONCLUSIONS
- TMLA has low toxicity to *Scenedesmus subspicatus*.

DATA QUALITY
- Reliability: Klimisch Code = 1.

REFERENCES
- Knacker et al., 1993. A Study of the Toxcity to Algae (*Scenedesmus subspicatus*) of Trimellitic Anhydride. Study Number: BE-EA-128-91-02-ALG-1.

OTHER

ACUTE TOXICITY TO AQUATIC INVERTEBRATES (*e.g.*, DAPHNIA)

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)
- Remarks: 98% pure

METHOD
- Method/guideline: OECD 202, Part I
- Test type: Acute toxicity test
- GLP: Yes
- Year (study performed): 1991
- Species/Strain: *Daphnia magna* (Straus), water-flea
- Test details: static
- Statistical methods: Probit analysis. When less than three test substance concentrations caused immobilization between 0% and 100% the geometrical mean was used to determine the EC_{50}.
- Analytical monitoring: High performance thin-layer chromatography apparatus (HPTLC). The sample was treated with sodium hydroxide to hydrolyze the test substance completely. The alkaline solution was acidified with hydrochloric acid and evaporated to dryness under nitrogen. The residue was treated with diazomethane to form trimellitic acid trimethylester. The analyte was measured using HPTLC.
- Exposure period: 48 hours
- Remarks: TMA hydrolyzes to trimellitic acid (TMLA) in water. Test solutions were neutralized using sodium hydroxide. Therefore the test material was trimellitic acid and its sodium salt.

RESULTS
- Nominal concentrations: 130, 220, 350, 600, and 1,000 mg/L
- Measured concentrations: 21-82% (average of 52.5%)
- Unit:
- EC50, EL50, LC0, LL0, at 48 hours: Based on nominal concentrations: EC_0=1,000 mg/L, EC_{50}=could not be determined, NOEC >= 1,000 mg/L. Based on measured average concentration: EC_0=>792 mg/L
- Statistical results: descriptive
- Remarks:

CONCLUSIONS
- TMA has low toxicity to *Daphnia magna*.

DATA QUALITY
- Reliability: Klimisch Code=1

REFERENCES
- Knacker *et al.*, 1992. A Study of the Acute Immobilisation to *Daphnia* of Trimellitic Anhydride. Study Number: BE-EA-128-91-02-DAK-1.

OTHER

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)

METHOD
- Method/guideline: Acute oral toxicity
- Type (test type): lethality study
- GLP: Yes
- Year (study performed): 1991
- Species/Strain: Sprague-Dawley Rats
- Sex: male/female
- No. of animals per sex per dose: five male and five females at each dose.
- Vehicle: corn oil
- Route of administration: oral (gavage)
- Remarks: TMA was administered to the animals via oral gavage at doses of 2,000, 3,500, and 5,000 mg/kg body weight. The rats were observed for 14 days following test article administration.

RESULTS
- LD_{50} Value: 2,730 mg/kg for male and female combined (95% confidence limit 1,730 – 4,290 mg/kg). Separate LD_{50} values derived for males (3,340 mg/kg) and females (2,030 mg/kg) suggest sex-specific differences affect toxicity.
- Number of deaths at each dose level: 2/10 (2 females), 7/10 (2 males, 5 females), and 10/10 at the 2,000, 3,500, and 5,000 mg/kg dosage levels, respectively. Death generally occurred between 1 and 48 hours after exposure.
- Remarks: Prominent clinical signs observed included hypoactivity, ataxia, hypothermia, lacrimation, salivation, redness around the nose, discoloration around the mouth, wet/discolored inguinal fur and discolored paws. Surviving rats appeared normal three days following exposure.

Incidence of Stomach Lesions (n=5)

			Stomach			Small Intestine		Large Intestine	
Dose mg/kg	**Death**	**Mean Body Weight Change (g)**	**Discolored**	**Distended**	**Ulcerated**	**Discolored**	**Distended**	**Discolored**	**Distended**
2,000	2f	38m, 33f	1m, 1f	1f	2f	1f	1m, 1f	1f	1m, 1f
3,500	2m, 5f	119m, *	2m, 5f	2m, 2f	2m, 3f	0	0	0	0
5,000	5m, 5f	**	5m, 5f	4m, 5f	4m, 5f	2m	4m	1m	3m

*no female survivors
**no survivors
m – male
f – female

CONCLUSIONS

- The acute oral LD_{50} of TMA is 2,730 mg/kg for males and females combined.

REMARKS

- The acute oral toxicity study was chosen as the key study because it represents the highest dose tested in the battery of acute toxicity studies, though all acute studies were considered valid.

DATA QUALITY

- Reliability: Klimisch Code=1

REFERENCES

- IIT Research Institute. 1991. Acute Oral Toxicity Study of Trimellitic Anhydride in Rats. IITRI Project No. L08100, Study No. 1699.

OTHER

- Acute LD_{50} via dermal administration in rabbits: >2,000 mg/kg (IITRI, 1991).
- Acute LD_{50} via inhalation in rats: >2.33 mg/l in both male and females (IITRI, 1992)

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE

- Trimellitic anhydride (TMA)
- Remarks: 98.0 % pure

METHOD

- Method/guideline: Primary Eye Irritation
- Type (test type): Eye irritation
- GLP: No
- Year (study performed): 1991
- Species/Strain: New Zealand Albino rabbit
- Sex: male/female
- No. of animals per sex per dose: 1 male
- Vehicle: none
- Concentrations: 0.1 grams of undiluted TMA
- Remarks: It was anticipated that TMA might be a severe eye irritant. Therefore, out of concern for animal pain and discomfort, only one rabbit was used initially as a test subject. TMA was administered undiluted at a dose of 0.1 grams into one eye with the other eye serving as the untreated control. The treated eye was scored for irritation at 1, 2, 3, 4, 7, and 14 days following test article administration. Irritation was scored using the Draize method. A reaction was considered positive if at any observation period, the test article produced ulceration or opacity of the cornea (cornea score > than 0), inflammation or slight circumcorneal injection of blood vessels of the iris (iris score > 0), any obvious conjunctival swelling with partial eversion of the lids (chemosis score 2 or greater), or conjunctival erythema of diffuse crimson red (erythema score 2 or greater) with individual vessels not easily discernable

RESULTS

Signs of ocular irritation were maximum (i.e. Draize score 110/110) at the 24 hour examination and the study was terminated immediately thereafter with no dosing of any additional animals.

The maximum eye irritation score of 110/110 was obtained 1 day after administration of test article.

CONCLUSIONS

- TMA is severely irritating to eyes.

DATA QUALITY

- Reliability: Klimisch Code= 2 (score based on only one animal, study terminated early)

REMARK

REFERENCES

- IIT Research Institute. 1991. Primary Eye Irritation Study of TMA in Rabbits. Study No. 1693

OTHER

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE

- Trimellitic anhydride (TMA)
- Remarks: 98.0 % pure

METHOD

- Method/guideline: Acute Dermal Irritancy/Corrosivity Study
- Type (test type): skin irritation
- GLP: Yes
- Year (study performed): 1991
- Species/Strain: New Zealand White rabbit
- Sex: male/female
- No. of animals per sex per dose: 3 males and 3 females
- Vehicle: none
- Concentrations: 0.5 grams of undiluted TMA
- Remarks: TMA was administered undiluted at a dose of 0.5 grams to the shaved, pre-moistened (with water) backs of six rabbits. The application site was covered with an adhesive dressing. After 4 hours the dressings were removed, the application site was rinsed with a light mineral oil and rubbed gently with a paper towel to remove residual test article. The skin of the animal was scored for irritation at 30-60 minutes, 24, 48, and 72 hours and 7 and 14 days following removal of the wrappings. Skin reactions were graded according to the Draize method.

RESULTS

Summary of Dermal Irritation Scores

	30-60 min	24 hr	48 hr	72 hr	7 days	14 days
Mean Edema score	1.8	1.0	0.3	0.3	0.0	0.0
Mean erythema and or eschar formation score	2.5	1.2	1.0	0.8	0.7	0.0
Irritation score*	4.3	2.2	1.3	1.1	0.7	0.0

*Irritation score = mean edema score + mean erythema score

The dermal irritation score ranged from 4.3/8.0 at 30-60 minutes following unwrapping to 0.0/8.0 at 14 days. The primary dermal irritation score (PDIS) for trimellitic anhydride was 1.7 (erythema/eschar formation + edema at 24 hours)+ (erythema/eschar formation + edema at 72 hours)/ 2 = PDIS

CONCLUSIONS

- TMA is a mild skin irritant.

REMARKS

- Because the skin of the test animals was premoistened with water, at least some of the TMAwaslikely converted to TMLA upon contact.

DATA QUALITY

- Reliability: Klimisch Code= 1

REMARK.

REFERENCES

- IIT Research Institute. 1991. Acute Dermal Irritancy/Corrosivity Study of Trimellitic Anhydride in Rabbits. Study No. 1694

OTHER

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE

- Trimellitic anhydride (TMA)
- Remarks: 98.0 % pure

METHOD

- Method/guideline: Dermal Sensitization
- Type (test type): Dermal Sensitization.
- GLP: Pre GLP
- Year (study performed): 1987
- Species/Strain: Hartley Guinea Pig
- Sex: male
- No. of animals per sex per dose: 10 males
- Vehicle: Dimethyl sulfoxide induction phase, acetone challenge phase
- Concentrations: 30% w/v induction, 5% w/v challenge phase
- Remarks: Induction - 0.3 ml of a 30% solution of TMA in dimethylsulfoxide was applied to the backs of 10 guinea pigs once per week for three weeks. Dosing material was held in place using an elastic adhesive bandage. All wrappings were removed 6 hours after each application. Challenge – Two weeks following the last induction phase dose a 0.3 ml quantity of a 5% TMA in acetone was applied to the backs of ten treated and ten control animals. Test article was held in place for 6 hours. A second challenge dose was applied in the same manner one week later. Approximately 24 and 48 hours after removal of each challenge patch, the test sites were scored for edema and erythema according to the method of Draize. A reaction with a Draize erythema score of 2 or greater in the treated animals was considered a positive response. The concentration of test article used during the challenge phase was intended to produce a Draize erythema reaction of 1 or less in control animals.

STATISTICS

- (Bishop, Fineberg, and Holland Discrete Multivariate Analysis, 1975)

RESULTS

Positive erythema reactions (score > 2) were observed in seven treated guinea pigs following the first challenge, while none of the control guinea pigs exhibited similar reactions. However, after the 2nd challenge, the majority of treated and control animals exhibited a positive reaction. Statistically, the main effect of treated vs control and 1st vs 2nd challenge were significant, while the time of scoring was not a factor.

Number of animals per erythema score

		Time of Scoring									
		24 Hours					**48 Hours**				
		Erythema Score					**Erythema Score**				
Group	**Challenge**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Treated	1	2	4	2	2	0	1	2	4	3	0
Treated	2	0	3	5	2	0	0	3	4	3	0
Control	1	10	0	0	0	0	10	0	0	0	0
Control	2	0	3	6	1	0	0	3	6	1	0

CONCLUSIONS

- TMA caused a positive dermal sensitization response in guinea pigs.

DATA QUALITY

- Reliability: Klimisch Code= 1

REMARK

- The use of solvents appear to increase the dermal sensitization potential of TMA, presumable by increasing uptake.

REFERENCES

- IIT Research Institute. 1987. Dermal Sensitization Study of Trimellitic anhydride in Guinea Pigs. Study No. 1196

OTHER

- IITRI 1993 TMA applied neat did not cause a positive sensitization response.

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE

- Trimellitic anhydride (TMA)
- Remarks: 98.0 % pure

METHOD

- Method/guideline: Modified Buehler Dermal Sensitization
- Type (test type): Dermal Sensitization.
- GLP: Yes
- Year (study performed): 1993
- Species/Strain: Hartley Guinea Pig
- Sex: male
- No. of animals per sex per dose: 10 males
- Vehicle: None
- Remarks: Induction - 0.3 g TMA was applied to the backs of 10 guinea pigs once per week for three weeks. Dosing material was held in place using an elastic adhesive bandage. All wrappings were removed 6 hours after each application. Challenge – Two weeks following the last induction phase dose a 0.3 g TMA was applied to the backs of ten treated and ten control animals. Test article was held in place for 6 hours. A second challenge dose was applied in the same manner 13 days later. Approximately 24 and 48 hours after removal of each challenge patch, the test sites were scored for edema and erythema according to the method of Draize. A reaction with a Draize erythema score of 2 or greater in the treated animals was considered a positive response. The amount of test article used during the challenge phase was intended to produce a Draize erythema reaction of 1 or less in control animals.

STATISTICS

- (Bishop, Fineberg, and Holland Discrete Multivariate Analysis, 1975)

RESULTS

Positive erythema reactions (score $\geq$ 2) were not observed in any treated or sham animals following either challenge dose.

Number of animals per erythema score

		Time of Scoring									
		24 Hours Erythema Score					**48 Hours Erythema Score**				
Group	**Challenge**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Treated	1	7	3	0	0	0	9	1	0	0	0
Sham	1	10	0	0	0	0	10	0	0	0	0
Treated	2	10	0	0	0	0	10	0	0	0	0
Sham	2	9	1	0	0	0	10	0	0	0	0

CONCLUSIONS

- TMA applied neat did not cause a positive dermal sensitization response in guinea pigs.

DATA QUALITY

- Reliability: Klimisch Code = 1

REMARK

- The use of solvents appear to increase the dermal sensitization potential of TMA, presumable by increasing uptake.

REFERENCES

- IIT Research Institute. 1993. Dermal Sensitization Study of Trimellitic anhydride in Guinea Pigs Using the Modified Buehler Method. Study No. 1

OTHER

- IITRI 1987 TMA applied in DMSO during the induction phase and in acetone during the challenge phase caused a positive dermal sensitization response.

GENETIC TOXICITY ELEMENTS

GENETIC TOXICITY IN VITRO (CHROMOSOMAL ABERRATIONS)

TEST SUBSTANCE

- Trimellitic Anhydride (TMA)

METHOD

- Method/guideline: Chromosomal Aberrations in Chinese Hamster Ovary Cells (CHO) with Confirmation (Evans, 1976; Preston *et al.*, 1981) (OECD 473)
- Type (test type): mammalian cell aberration assay
- GLP: Yes
- Year (study performed): 1991
  Cells: Chinese Hamster Ovary
- Concentration levels: 260, 520, 1,040, and 2,080 ug/ml
- Exposure period: 14 hours (non activated study), 12 hours (S-9 activation study)
- Statistical methods: Fisher's exact test
- Remarks: Dose selection was limited by the insolubility of TMA in solvent at concentrations exceeding 2,080 ug/ml. In order to maintain neutrality, the pH of test concentrations 520, 1040, and 2080 ug/ml were adjusted to approximately pH 7.
- Culture Conditions: CHO cells were seeded at approximately $5x10^5$ cells/25 cm^2 flask and were incubated at 37±1ºC in a humidified atmosphere of 5±1% CO_2 in air for 16-24 hours. All dose levels were run in duplicate.
- Control groups: triethylenemlamine (TEM), cyclophosphamide (CP), dimethylsulfoxide (DMSO)
- Criteria for evaluating results: Toxicity measured by mitotic inhibition.

RESULTS

- Mitotic inhibition relative to solvent control was approximately 41% at the highest dose tested (2080 ug/ml).
- Chromosomal Aberrations
- With metabolic activation: negative
- Without metabolic activation: negative

CONCLUSIONS

- TMA was concluded to be negative in the CHO cytogenics assay

DATA QUALITY

- Reliability: Klimisch Code=1

REFERENCES

- Putnam and Morris. 1991. Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. Microbiological Associates, Inc. Laboratory Study Number: TA039.337100

OTHER

GENETIC TOXICITY IN VITRO (HGPRT Mutation Assays)

TEST SUBSTANCE

- Trimellitic Anhydride (TMA)

METHOD

- Method/guideline: CHO/HGPRT Mutation Assay with Confirmation (OECD 476)
- Type (test type): Mutation assay
- GLP: Yes
- Year (study performed): 1991
- Cells: Chinese Hamster Ovary
- Concentration levels: 500, 750, 1,000, 1,500, 2,000 mg/L
- Exposure period: Cells were exposed in duplicate to five concentrations of the test article for 5 hours at 37+1ºC
- Statistical methods: Descriptive
- Remarks: Dose levels were selected following a preliminary toxicity test. Toxicity was based on cloning efficiency after treatment relative to the solvent control. Cells were exposed to nine concentrations of test article ranging from 0.18 to 1786 ug/ml. The two highest concentrations (536 and 1786 ug/ml) required pH adjustment with sodium hydroxide to achieve neutrality. The maximum dose selected and the solubility achieved for the assay was based on heating test article in solvent to 37C as an aid to solubilization. The highest dose selected was based on limited solubility of the test article in solvent and effects on pH and osmolality.
- Control groups: ethyl methanesulfonate, benzo(a)pyrene, dimethylsulfoxide (DMSO)
- Culture conditions: Exponentially growing cells were seeded at a density of $5x10^5$ cells/25 cm^2 flask and incubated at 37$\pm$1ºC in humidified atmosphere for 5$\pm$1% CO_2 for 18-24 hours.
- Criteria for evaluating results: Assay considered positive in the event of a dose-dependant increase in mutant frequencies with at least two consecutive doses showing mutant frequencies that are elevated above 40 mutants per 10^6 clonable cells. The test was considered valid if the cloning efficiency of the solvent and untreated controls was greater than 50%. The spontaneous mutant frequency in the solvent and untreated controls must fall within the range of 0-25 mutants per 10^6 clonable cells. The positive control must induce a mutant frequency at least three times that of the solvent control and must exceed 40 mutants per 10^6 clonable cells.

RESULTS

- Chromosomal Aberrations
- With metabolic activation: negative
- Without metabolic activation: negative

CONCLUSIONS

- Under the conditions of this report, TMA was found to be negative in both the absence and presence of exogenous metabolic activation.

DATA QUALITY

- Reliability: Klimisch Code=1

REFERENCES

- Bigger and Sigler. 1991. CHO/HGPRT Mutation Assay with Confirmation. Microbiological Associates, Inc. Laboratory Study Number: TA039.332001

OTHER

GENETIC TOXICITY *IN VITRO* (GENE MUTATIONS)

TEST SUBSTANCE

- Trimellitic anhydride (TMA)

METHOD

- Method/guideline: Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay with a Confirmatory Assay (OECD 471)
- Type: Bacterial Mutation Reversion Assay
- System of testing: Bacterial
- GLP: Yes
- Year (study performed): 1991
- Cell line: *Salmonella typhimurium* TA98, TA1535, TA1537, TA1538, TA100.
- Metabolic activation: Liver S-9, Aroclor-induced
- Species: Rat
- Concentrations tested: 0, 33, 100, 333, 1,000, 3,333, 10,000 µg/plate
- Statistical Methods: Descriptive
- Number of replicates: 3
- Positive and negative control groups and treatment: 2-aminofluorene, 9-aminoacridine, sodium azide, 2-nitrofluorene, dimethylsulfoxide (DMSO)
- Criteria for evaluating results (*e.g.* cell evaluated per dose group): For the test article to be positive, it must cause a dose-related increase in the mean revertants per plate of at least one tester strain with a minimum of two increasing concentrations of test article. Data sets for strains TA1535, TA1537 and TA1538 were judged positive if the increase in mean revertants at the peak of the dose response was equal or greater than three times the mean vehicle control value. For strains TA98 and TA100 results were considered positive if the increase in mean revertants at the peak dose was equal to or greater than two times the mean vehicle control.

RESULTS

- Genotoxic effects
- With metabolic activation: negative
- Without metabolic activation: negative

CONCLUSIONS

- TMA did not cause a positive response in the Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay with a Confirmatory Assay.

DATA QUALITY

- Reliability: Klimisch Code= 1

REFERENCES

- San and Wagner. 1991. Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay. Microbiological Associates, Inc. Laboratory Study Number TA039.501014.

OTHER

REPEATED DOSE TOXICITY

TEST SUBSTANCE

- Trimellitic Anhydride (TMA)

METHOD

- Method/guideline followed: 13-week inhalation toxicity study
- Test type: Subchronic inhalation toxicity test
- GLP (Y /N): Yes
- Year (study performed): 1988
- Species: Rat
- Strain: Sprague Dawley
- Route of administration: inhalation (particulate aerosol)
- Duration of test: 13 weeks
- Doses/concentration levels: 0, 0.002, 0.015, or 0.054 mg/m^3
- Sex: male & female
- Exposure period: 6.5 or 13 weeks
- Frequency of treatment: 5 days/week
- Control group and treatment:
- Post exposure observation period: 3 or 38 weeks
- Statistical methods: Bartlett's test, ANOVA, Duncan's multiple range test.
- Remarks field for Test Conditions.
- Test Subjects
- Age at study initiation: 10 weeks
- No. of animals per sex per dose: 10
- Study Design
- Vehicle:
- Clinical observations performed and frequency: daily
- Organs examined at necropsy: Liver, kidneys, adrenal glands, spleen, thymus, trachea, lungs, heart, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, salivary glands, urinary bladder, pituitary gland, thyroid glands, parathyroid glands, mesenteric lymph nodes, bone marrow, brain, sex organs, and gross lesions. Serum antibody levels determined

RESULTS

- NOAEL (NOEL): --
- LOAEL (LOEL): 0.002 mg/m3
- Toxic response/effects by dose level:

	6.5 weeks		13 weeks		
Concentration (mg/m^3)	**Serum Antibody Levels (ng rat serum albumem bound/mL serum)** **M**	**Lung foci (incidence)** **M**	**Serum Antibody Levels (ng rat serum albumem bound/mL serum)** **M F**		**Lung foci (incidence)** **M F**
0.0	5.05	1/10	0.7	3.4	6/10 4/10
0.002	171.5	7/10	78.4	39.8	6/10 2/10
0.015	335.6	9/10	85.5	43.7	9/10 9/10
0.054	402.1	10/10	102.6	55.8	10/10 8/10

Remarks field for Results:

CONCLUSIONS

- Three groups of ten male and ten female Sprague Dawley rats each were exposed to TMA via inhalation for 6.5 or 13 weeks. Recovery times of 0, 3, and 38 weeks were evaluated. No treatment related deaths were observed. The lung appeared to be the only tissue affected, resulting in treatment-related effects (increased lung weight and volume, external hemorrhagic foci, inflammatory cell infiltration, and bronchoalveolar pneumonia) that were more severe in rats from the 6.5-week treated group than observed in similarly treated male and female rats exposed for 13 weeks. Antibody levels and lung foci were elevated in a dose-dependent manner, beginning at the lowest dose tested. Pulmonary physiology parameters were unaffected. The results at 13 weeks are in contrast to the more severe effects observed following 6.5 weeks of exposure under the same conditions, suggesting some degree of adaptation (immunologic tolerance). Minimal effects were observed in the 3 and 38-week recovery groups.

DATA QUALITY

- Reliability: Klimisch Code= 1

REFERENCES

- IITRI. 1988. Thirteen-week inhalation toxicity study of trimellitic anhydride in rats. Final
- Report. IIT Project No. L8100, Study No. 899, Test Article No. 128.

OTHER

TOXICITY TO REPRODUCTION

TEST SUBSTANCE

- TMA

METHOD

- Method/guideline followed: ?
- Test type: Subchronic oral toxicity test
- GLP (Y/N): Pre GLP
- Year (study performed): 1970
- Species: Rat
- Strain: albino
- Route of administration: feed
- Duration of test: 90 days
- Doses/concentration levels: 0, 10,000 ppm
- Sex: male & female
- Exposure period: 90 days
- Frequency of treatment: daily
- Test Subjects
- Age at study initiation: not specified
- No. of animals per sex per dose: 10 male, 10 female / per dose
- Study Design
- Vehicle: feed
- Clinical observations performed and frequency: Daily
- Organs examined at necropsy: Histopathological analysis included the following reproductive tissues: ovary, uterus, testes, seminal vesicle. Other tissues examined included esophagus, stomach (cardia, fundus and pylorus) small intestine (duodenum, jejunum and ileum), cecum, colon, liver, kidneys, spleen, pancreas, urinary bladder, pituitary gland, adrenal gland, bone marrow,, thyroid, parathyroid, salivary gland, prostate, heart, aorta, lung, lymph node (cervical and mesenteric), skeletal muscle, peripheral nerve, bone (femur), spinal cord, trachea, eye, optic nerve and brain (cerebrum, cerebellum and pons).

RESULTS

- No statistically significant differences between test and control animals were noted for body weights, food consumption, hematological parameters, blood chemistry, urinalysis, gross or microscopic histopathology, organ weights, organ to body weight and organ to brain weight ratios. No untoward behavioral reactions or test article related mortality was noted among any of the animals included in the study. 10,000 ppm in feed was identified as a NOAEL. Assuming a default feed intake of 0.05 kg feed/kg body weight per day, this feed concentration corresponds to a dose of approximately 500 mg/kg-day.

CONCLUSIONS

- TMA does not produce histopathological effects in reproductive tissues following subchronic oral exposures to high doses. The NOAEL was greater than 10,000 ppm or approximately 500 mg/kg/day.

DATA QUALITY

- Reliability: Klimisch Code = 1

REFERENCES

Industrial Bio-Test Laboratories. 1970. Report to standard oil company (Indiana): Ninety-day subacute oral toxicity of LM 3813 in albino rats. IBT B7989.

Hill Top Research. 1969. Thirteen week dietary administration of trimellitic anhydride to rats. S-192.

Hill Top Research. 1969. Dietary administration of trimellitic anhydride to dogs for 13 weeks. S-260.

OTHER

- Although a multigenerational reproductive toxicity test was not located for TMA, data available from other studies suggest that the potential for significant toxicity to reproduction from TMA exposures is low.

- Subchronic inhalation exposures of male and female rats to TMA concentrations of 0.002, 0.015, or 0.054 mg/m^3 did not result in any histopathological effects to reproductive tissues (IITRI, 1988).

- Additionally, reproductive performance was not affected in female rats and guinea pigs following exposure to TMA concentrations of 0.5 mg/m^3 on days 6 through 15 of gestation (Ryan, 1988).

- Oral exposures to TMA in the diet at concentrations of 1,000, 10,000 or 20,000 ppm for 13 weeks did not produce any histopathological effects in the reproductive tissues (gonads) of male and female beagle dogs (4 per dose level) (Hill Top Research, 1969). Assuming a default feed intake of 0.025 kg feed/kg bodyweight per day, the highest concentration corresponds to a dose of approximately 500 mg/kg-day.

- Oral exposures to TMA in the diet at concentrations of 1,000, 5,000 or 10,000 ppm for 13 weeks did not produce any histopathological effects in the reproductive tissues (gonad, uterus) of male and female rats (20 per dose level) (Hill Top Research, 1969). Assuming a default feed intake of 0.05 kg feed/kg bodyweight per day, the highest concentration corresponds to a dose of approximately 500 mg/kg-day.

DEVELOPMENTAL TOXICITY/TERATOGENICITY

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)

METHOD
- Method/guideline: Teratological Evaluation - Inhalation
- GLP: No
- Year (study performed): 1988
- Species: Rat, Guinea Pig
- Strain: Sprague-Dawley (rat), Hartley (guinea pig)
- Route of administration: inhalation
- Doses/concentration levels: 0 and 0.50 mg/m^3
- Sex: Female
- Exposure period: Gestation days 6-15 (rats), 6-26 (guinea pigs)
- Frequency of treatment: Daily
- Control group and treatment: filtered air
- Duration of test: 6 hours/day
- Statistical methods: t-test, ANOVA-
- Remarks: Dams were divided into two groups the first group was sacrificed one day prior to parturition for teratologic evaluation and the second group was sacrificed after weening. Groups of offspring were exposed to a challenge dose of TMA either as neonates or as adults to assess the effect of in utero exposure to TMA on immune status.

Number of Dams per Study Group

	Teratology		Parturition	
Species	Control	TMA Exposed	Control	TMA Exposed
Rat	12	11	15	16
Guinea Pig	8	7	8	7

RESULTS
- Exposure conditions: The time-weighted average exposure concentration was 497.1 ug/m^3. The range of the average particle size was 2.73 – 2.85 microns, with 99.99% of the particles being less than 10 microns.
- Maternal toxicity: No significant effects were detected in gravid uterus weights or in body weights for either species. Lung foci and TMA-specific antibody were observed inall exposed dams.
- Developmental toxicity: No significant differences in body weights were detected between the fetuses in the treated and control groups. No significant variations or malformations were observed in the gross external appearance, viscera, skeletal system, or development of the brain in either species.
- TMA specific antibody was also noted in neonatal rats but not neonatal guinea pigs. TMA specific antibodies were not significantly elevated in adult offspring. Lung foci were only observed in the challenged rat offspring of mothers that had not completely recovered from the original TMA exposure (Day 15 exposure). Lung foci were not observed in adult offspring after challenge.

CONCLUSIONS
- No treatment-related effects were observed in maternal, fetal, or offspring body weights, or litter viability in either species. No teratogenic effects were observed in either species.

DATA QUALITY

- Reliability: Klimisch Code= 1

REFERENCES

- Ryan, B.M. 1988. Teratological Evaluation of Trimellitic Anhydride (TMA) in Rats and Guinea Pigs. Submitted in partial fulfillment of the requirements for the degree of Master of Science in Biology in the School of Advanced Studies of Illinois Institute of Technology.

OTHER

SIDS DOSSIER TRIMELLITIC ACID (TMLA)
CAS No. 528-44-9

Sponsor Country: U.S.A.

DATE: January, 2002

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. CAS-Number:: 528-44-9

B. Name *(IUPAC name)*: Trimellitic acid

C. Name *(OECD name)*: Trimellitic acid

D. CAS Descriptor

F. EINECS-Number

F. Molecular Formula: C9H6O6

G. Structural Formula

H. Substance Group

I. Substance Remark

J. Molecular Weight: 210.14

1.02 OECD INFORMATION

A. Sponsor Country: U.S.A.

B. Lead Organisation:
Name of Lead Organisation: BP-Amoco Chemicals
Contact person: David Dutton
Address:

U.S.A.
Tel:
Fax:

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance element [ ]; inorganic [ ]; natural substance [ ]; organic [X];
organometallic [ ]; petroleum product [ ]

B. Physical State *(at 20°C and 1.013 hPa)*
gaseous [ ]; liquid [ ]; solid [X]

C. Purity *(indicate the percentage by weight/weight)* >98%

1.2 SYNONYMS: 1,2,4-benzenetricarboxylic acid

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

Although production estimates are not available for TMLA, it is used to make trimellitic anhydride for which the following production estimates have been made:

65,000 metric tonnes/year produced in U.S.
30,000 metric tonnes/year outside U.S.
Reference: SRI, 2000; ChemSystems, 2000

50,000 tonnes per annum in 1990
Reference IPCS, 1992

>2.27x106 g/year in the 1970s
Reference: HSDB, 2001

1.6 LABELLING AND CLASSIFICATION

Labelling
Type:
Specific limits:
Symbols:
Note:
R-phrases:
S-phrases:
Text of S-phrases:
Remarks:

Classification
Type:
Category of danger:

R-phrases:
Remarks:

1.7 USE PATTERN

A. General: 100% used in production of trimellitic anhydride

B. Uses in Consumer Products: none

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

1.9 SOURCES OF EXPOSURE

1.10 ADDITIONAL REMARKS

A. Options for disposal

B. Other remarks

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

(a)

Value:	219°C
Decomposition:	Yes [ ] No [ ] Ambiguous [ ]
Sublimation:	Yes [ ] No [ ] Ambiguous [ ]
Method:	Other
GLP:	Yes [ ] No [ ] ? [x]
Remarks:	Estimated
Reference:	SRC, 2001

2.2 BOILING POINT

(a)

Value	
Decomposition	
Sublimation	
Method	
GLP	
Remarks:	Upon heating, trimellitic acid is converted to trimellitic anhydride and water prior to boiling. The boiling point of trimellitic anhydride is 390º C.

2.3 DENSITY

No data available

2.4 VAPOUR PRESSURE

(a)

Value:	3.8×10^{-6} Pa (2.88×10^{-8} mm Hg)
Temperature:	25^{o}C
Method:	calculated [X]; measured [ ] Year:
GLP:	Yes [ ] No [ ] ? [x]
Remarks:	
Reference:	Neely and Blaue, 1985

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

(a)
Log Pow: 0.95 – trimellitic acid (TMLA)
Temperature: 25º C
Method: calculated [X]; measured [ ]
GLP: Yes [ ] No [ ] ? [ ]
Remarks: Calculated using QSAR software KOWWIN
Test Substance Trimellitic acid
Reference: KOWIN Version 1.66.2000.
(http://www.epa.gov/oppt/exposure/docs/episuitedl.htm)

(b)
Log Pow: 0.57
Temperature: 25º C
Method: calculate [X], measured []
GLP: Yes [], No [X], ?[]
Remarks:
Test Substance: Trimellitic acid
Reference: CLOGP Program (http://www.daylight.com)

(c)
Log Pow: 0.81
Temperature: 25º C
Method: calculated [X], measured []
GLP: Yes [], No [X], ?[]
Remarks:
Test Substance: Trimellitic acid
Reference: Interactive Analysis Program (http://www.logp.com)

(d)
Log Pow 0.78
Temperature: 25º C
Method: calculated [X], measured []
GLP: Yes [], No [X], ?[]
Remarks:
Test Substance: Trimellitic anhydride
Reference: ALOGP Program
(http://www.ihn.unil.ch/Appl/cchem2.html)

(e)
Log Pow 0.87
Temperature: 25º C
Method: calculated [X], measured []
GLP: Yes [], No [X], ?[]
Remarks:
Test Substance: Trimellitic anhydride

Reference: XLOGP Program (ftp2.ipc.pku.edu.cn

2.6 WATER SOLUBILITY

A. Solubility

(a)
Value: 21,000 mg/L
Temperature: 25ºC
Description: Miscible[ ]; Of very high solubility [ ];
Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ];
Of low solubility [X]; Of very low solubility [ ]; Not soluble [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [ ]
Remarks:
Reference: SRC, 2001

2.7 FLASH POINT *(liquids)*

No data available

2.8 AUTO FLAMMABILITY *(solid/gases)*

No data available

2.9 FLAMMABILITY

No data available

2.10 EXPLOSIVE PROPERTIES

No data available

2.11 OXIDIZING PROPERTIES

No data available

2.12 ADDITIONAL REMARKS

No additional remarks

2.13 ADDITIONAL DATA

No additional data

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

(a)

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Light source:	Sun light [ ]; Xenon lamp [ ]; Other [ ]
Light spectrum:	
Relative intensity:	
Concentration of Substance:	
Temperature:	
Direct photolysis:	
Half life:	6.55 days
Degradation:	
Quantum yield:	
Method:	calculated [X]; measured [ ]
	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Trimellitic acid
Remarks:	Reaction rate with photo-chemically produced hydroxyl radicals estimated ($1.63x10^{-12}$ cm^3/mol-s)
Result:	
Reference:	AOPWIN (SRC, 2001)

3.1.2 STABILITY IN WATER

(a)

Type	
Half-life	
Degradation	
GLP	
Test substance	
Remarks	Based on the chemical structure, trimellitic acid is no expected to undergo abiotic hydrolysis in the environment.
Reference	

3.1.3 STABILITY IN SOIL

No data available

3.2 MONITORING DATA (ENVIRONMENT)

No data available

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

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

No data available

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media: Air-biota [ ]; Air-biota-sediment-soil-water [X]; Soil-biota [ ];
Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]

Method: Fugacity level I [X]; Fugacity level II [X]; Fugacity level III [X];
Fugacity level IV [ ]; Other (calculation) [ ]; Other (measurement)[ ]

Results:

	Level I	**Level II**	**Level III**
Air	7.68E-7%	7.68E-7%	3.46E-6%
Water	99.2%	99.2%	50.6%
Soil	0.78%	0.7852.1%	49.3%
Sediment	0.02%	0.02%	0.02%

Remarks: Default release estimates assumed
Reference: Trent University, 1999

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Results:
Remarks:
Reference:

3.5 BIODEGRADATION

(a)
Type: aerobic [X]; anaerobic [ ]
Inoculum: adapted [ ]; non-adapted [ ]; ? [ ]; sewage [X]
Concentration: 10.19 mg/l related to COD [ ]; DOC [X]; Test substance [ ];

Medium:	water [ ]; water-sediment [ ]; soil [ ]; sewage treatment [X]
Degradation:	>60% within 7 days
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; under test condition no biodegradation observed [ ], Other [ ]
Method:	OECD Guideline 301 B, Modified Sturm-Test
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic anhydride
Remarks:	Sewage microorganisms from a sewage plant working with predominantly domestic sewage used as the inoculum.
Reference:	Lebertz, 1991a

(b)

Type:	aerobic [X]; anaerobic [ ]
Inoculum:	adapted [ ]; non-adapted [ ]; ? [ ]; sewage [X]
Concentration:	100 ppm related to COD [ ]; DOC [ ]; Test substance [X];
Medium:	water [ ]; water-sediment [ ]; soil [ ]; sewage treatment [X]
Degradation:	89-101% over 4 weeks
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; under test condition no biodegradation observed [ ], Other [ ]
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Trimellitic anhydride
Remarks:	Since TMA rapidly hydrolyzes, this study assesses biodegradation of TMLA.
Reference:	Letz et al., 1987

3.6 BOD_5,COD OR RATIO BOD_5/COD

No data available

3.7 BIOACCUMULATION

No data available

3.8 ADDITIONAL REMARKS

No additional remarks

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	static [x]; semi-static [ ]; flow-through [ ]; other [ ]; open-system [ ]; closed-system [ ]
Species:	*Leuciscus idus melanotus* (Golden orfe)
Exposure period:	96 hr.
Results:	LC_0 (96 hr): > 1000 mg/L LC_{50} (96 hr): could not be determined. NOEC (96 hr): = 1000 mg/L based on nominal concentrations NOEC (96 hr): >896 mg/L based on the measured average concentration of the highest concentration level tested.
Analytical monitoring:	Yes [x] No [ ] ? [ ]
Method:	OECD Guideline for Testing of Chemicals No. 203 "Fish, Acute Toxicity Test", adopted April 4, 1984 and the "German Water Endangerment Classification Scheme, DIN 38 412, Part 15" adopted June 1982.
GLP:	Yes [x] No [ ] ? [ ]
Test substance:	It is thought that TMA was hydrolysed under test conditions. As a result, it is believed that under test conditions and after pH adjustments to the required physiological value TMLA and trimellitic sodium salt, respectively, were the test materials investigated in this study.
Remarks:	The highest concentration causing no mortality within the period of the range-finding test was 1000 mg/L. The lowest concentration causing 100% mortality within the period of the range-finding test was >1000 mg/L.
Reference:	Knacker *et al*., 1993.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

(a)

Type of test:	static [x]; semi-static [ ]; flow-through [ ]; other [ ]; open-system [ ]; closed-system [ ]
Species:	*Daphnia magna* (Straus)
Exposure period:	48 hr.
Results:	EC_0: >1000 mg/L

EC_{50}: could not be determined.
EC_0: >792 mg/L (based on the measured average concentration of the highest concentration level tested).

Analytical monitoring: Yes [ ] No [ ] ? [ ]

Method: OECD Guideline No. 202, Part I "Daphnia sp., Acute Immobilisation Test and Reproduction Test" adopted April 4, 1984.

GLP: Yes [x] No [ ] ? [ ]

Test substance: It is thought that TMA was hydrolysed under test conditions. As a result it is believed that under test conditions and after pH adjustments to the required physiological value TMLA and trimellitic sodium salt, respectively, were the test materials investigated in this study.

Remarks: Highest concentration causing no immobilization within the period of the range-finding test: 100 mg/L. The bwest test concentration causing 100% immobilization within the period of the range-finding test: > 100 mg/L.

Reference: Knacker, *et al.*, 1992.

4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

(a)

Species: *Scenedesmus subspicatus* (green algae)

End-point: Biomass [ ]; Growth rate [x]; Other [ ]

Exposure period: 96 hr.

Results: NOEC = 1000 mg/L based on nominal concentrations;
NOEC = 739 mg/L based on the measured average concentration of the highest concentration level tested.

Analytical monitoring: Yes [x] No [ ] ? [ ]

Method: OECD Guideline 201, 1984.

GLP: Yes [x] No [ ] ? [ ]

Test substance: It is thought that trimellitic anhydride was hydrolysed under test conditions. As a result it is believed that under test conditions and after pH adjustments to the required physiological value trimellitic acid and trimellitic sodium salt, respectively, were the test materials investigated in this study.

Remarks: The highest concentration tested caused no obvious inhibition of growth within the period of the range-finding-test relative to the control. An effect relative to the control could not be determined in any of the concentration levels tested.

Reference: Knacker et al., 1993

4.4 TOXICITY TO BACTERIA

(a)

Type:	Aquatic [ ]; Field [ ]; Soil [ ]; Other [x]
Species:	activated sludge
Exposure Period:	3 hr.
Results:	The range-finding study tested 1, 10, 100 mg/L and found no or minimal inhibition (6% at 100 mg/L). The definitive portion of the study tested 500 to 4000 mg/L and found complete inhibition at all concentrations tested. The following EC values were extrapolated from data derived from the definitive portion of the study only: EC_5: 0.095 mg/L EC_{25}: 1.1 mg/L EC_{50}: 5.7 mg/L EC_{75}: 30.4 mg/L EC_{95}: 340 mg/L However, data obtained from the two studies combined suggest that the actual EC_{50} falls in the range between 100 and 500 mg/L.
Analytical monitoring:	Yes [ ] No [ ] ? [X]
Method:	OECD-Test Guideline 209 "Activated Sludge, Respiration Inhibition Test"
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic anhydride. TMA was likely hydrolyzed to TMLA under the conditions of this assay.
Test Condition:	Activated sludge was added to the test solution and was aerated with compressed air for 3 hr. After the contact time, the solutions were poured into an oxygen-bottle and oxygen consumption was recorded for 10 minutes to determine respiration rates.
Reference:	Lebertz, 1991b

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

No data available, methods to extrapolate acute toxicity data to chronic exposures are readily available.

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

No data available

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data available

4.8 BIOTRANSFORMATION AND KINETICS

No data available

4.9 ADDITIONAL REMARKS

No additional remarks

5. TOXICITY

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/Sprague-Dawley
Value:	2,730 mg/kg
Method:	
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic anhydride administered 50% (w/v) suspension in corn oil. Because TMA is rapidly converted to TMLA in tissues, the acute effects of TMLA are considered to be similar to TMA.
Remarks:	Groups of ten male and ten female rats were administered 0, 2000, 3500, or 5000 mg/kg TMA via gavage. Animals were observed for 14 days following exposure. A 95% confidence limit of 1,730-4,290 mg/kg was reported for both sexes combined, with slightly lower values reported for females (2,030 mg/kg: CL=700-5,890 mg/kg) than for males (3,340 mg/kg: CL=1,740-6,410 mg/kg). Deaths generally occurred within 1-48 hours after exposure. Stomach lesions (thinning, ulcerations, hemorrhage, necrosis) were noted.
Reference:	IITRI, 1991a

5.1.2 ACUTE INHALATION TOXICITY

(a)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Rat/Sprague-Dawley
Exposure time:	4 hours
Value:	> 3,750 mg/m^3
Method:	Particulate
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic acid, average particle size = 7.7 microns (SD=0.38 microns).
Remarks:	Ten rats (five males; five females) were exposed to TMA particulate aerosol for four hours. No rats died during the study. Body weights were increased during the study. Gross necropsy revealed effects on the lung (red foci, mottled) and bladder (distended in one rat). Findings were considered of a minor nature and within normal limits.

Reference: IITRI, 1988b

5.1.3 ACUTE DERMAL TOXICITY

(a)

Type:	LD_0 [X]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [ ]
Species/strain:	Rabbit/New Zealand albino
Value:	2000 mg/kg
Method:	Single dose applied to 240 cm^2 patch
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Undiluted trimellitic anhydride. Because TMA is rapidly converted to TMLA in tissues, the acute effects of TMLA are considered to be similar to TMA.
Remarks:	Five male and five female rabbits received a single dermal dose of 2,000 mg/kg, applied for 24 hours. Animals were observed for 14 days following exposure. No deaths were observed. The authors concluded that the acute dermal LD_{50} value for TMA exceeds 2,000 mg/kg. Dermal irritation (erythema, edema) was observed in all animals immediately following the exposure, however, all animals recovered during the observation period. Body weights were slightly increased in females but unchanged in males. No treatment-related lesions were noted upon necropsy.
Reference:	IITRI, 1991b

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	5,600 mg/kg
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	TMA. Because TMA is rapidly converted to TMLA in tissues, the acute effects of TMLA are considered to be similar to TMA.
Remarks:	Study demonstrates a dermal LD50 of 5,600 mg/kg
Reference:	Rom, 1992.

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No data available

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

(a)

Species/strain: Rabbit/New Zealand White

Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ];
Irritating [ ]; Moderate irritating [ ]; Slightly irritating [X];
Not irritating [ ]

Classification: Highly corrosive (causes severe burns) [ ];
Corrosive (caused burns) [ ]; Irritating [X]; Not irritating [ ]

Method: 4-hours application of 0.5 g to a 240 cm^2 moistened skin patch

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

Test substance: Undiluted trimellitic acid

Remarks: Three male and three female rabbits were administered a single dermal TMLA dose of 0.5 g to a 240 cm^2 patch of pre-moistened skin for four hours (excess chemical removed with light mineral oil). Animals were monitored for 14 days following exposure. A primary dermal irritation score of 0.7 (maximum of 8) was reported for the first 60 minutes, however, effects generally reversed by the end of the observation period (72 hours). No signs of corrosivity were observed.

Reference: IITRI, 1988d

5.2.2 EYE IRRITATION/CORROSION

(a)

Species/strain: Rabbit

Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ];
Irritating [x]; Moderate irritating [ ]; Slightly irritating [ ];
Not irritating [ ]

Classification: Irritating [x]; Not irritating [ ]; Risk of serious damage to eyes [ ]

Method: Other

GLP: Yes [x] No [ ] ? [ ]

Test substance: Trimellitic acid

Remarks: Signs of ocular irritation reached a maximum (*i.e.*, Draize score = 59.7./110.0) at the 24-hour examination. Lackluster pitting and pannus formation were also observed.

Reference: Hatoum and Johnson, 1991.

5.3 SENSITISATION

(a)

Type:	Inhalation Sensitization
Species/strain:	Rat/Sprague-Dawley
Results:	Sensitizing [ ]; Not sensitizing [X]; ambiguous [ ]
Classification:	Sensitizing [ ]; Not sensitizing [X]
Method:	other
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Trimellitic Acid (TMLA)
Remarks:	The study consisted of two parts. The first part included three groups of ten male and ten female rats each, one group was exposed to TMLA (particulate aerosol) at 50 ug/m^3, six hr/day for five days. The remaining two groups were exposed only to filtered air. Following a three-week rest period, the TMLA-exposed group and one of the filtered air groups were challenged with 50 ug/m^3 TMLA for six hours. In the second part of the study, two groups of 12 male rats each were exposed to 50 ug/m^3 TMLA for six hr/day for five days. Following a three week rest period, one of the groups was challenged with a single inhalation exposure of 50 ug/m^3 TMA. None of the rats died and no significant clinical signs were noted during either part of the study. There were no statistically significant effects of treatment on body weight, lung weight and volume, foci or serum IgG antibody in either part of the study. Therefore, the authors concluded that TMLA did not induce respiratory sensitization in the rat nor did it have a cross-sensitization reaction with TMA.
Reference:	IITRI, 1989a

5.4 REPEATED DOSE TOXICITY

(a)

Species/strain:	Rat/Sprague-Dawley
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration:	Inhalation
Exposure period:	6 hrs/day
Frequency of treatment:	5 days/wk; 13 wks
Post exposure observation period:	18 hr to 4 weeks
Dose:	0, 50, 100, 300 ug/m^3
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	300 ug/m^3

LOEL: --
Method:
GLP: Yes [X] No [ ] ? [ ]
Test substance: TMLA
Remark: Four groups of rats were exposed to 0, 50, 100, and 300 ug/m^3 TMLA for six hrs/day, five days/wk for 13 wks. Ten rats/sex/group were retained for four weeks following the exposure to evaluate long-term effects. None of the rats died during the study. The exposed rats were comparable to the control rats in appearance and behaviour other than some salivation and redness around the eyes. There were no statistically significant effects of treatment on any body weight or organ weight parameter in any of the groups. TMLA and TMA-specific serum IgG antibody levels did not increase appreciably above the background levels established prior to exposure in the 300 ug/m^3 exposed group, so no immunotoxicologic response was apparent.
Reference: IITRI, 1989

(b)
Species/strain: Rat/CD(SD)BR
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Oral
Exposure period:
Frequency of treatment: 5 d/wk; 4 wks
Post exposure observation period:
Dose: 0, 100, 300, 1000 mg/kg
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [ ]; Concurrent vehicle [X]; Historical [ ]
NOEL: 300 mg/kg/day
LOEL: --
Method: OECD #TG-407, Repeated Dose Oral Toxicity – Rodent: 28-day or 14-day study, and Annex V B.7.
GLP: Yes [X] No [ ] ? [ ]
Test substance: Trimellitic acid (TMLA)
Remark: Groups of five male and five female rats received 0, 100, 300, or 1000 mg/kg/day of TMLA by oral gavage five days a week for approximately four weeks. No mortality or treatment-related changes in body weight, feed consumption, hematology, clinical chemistry parameters, organ weights, or histopathology were noted. Abnormal signs were restricted to diarrhea in the 1000 mg/kg male rats. At necropsy, all of the 1000 mg/kg/day animals had watery cecal contents and the cecum was distorted in a majority of the animals.

Reference: Hankinson and Sakal, 1991

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL IN VITRO TEST

(a)

Type: Mutagenicity
System of testing: *Salmonella* TA98, TA100, TA1535, TA1537
Concentration: 33, 100, 333, 1000, 3333, 10000 ug/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:
Cytotoxicity conc: 1000
Precipitation conc: --
Genotoxic effects:

	+	?	--
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: OECD 471
GLP: Yes [x] No [ ] ? [ ]
Test substance: TMA. Because TMA is rapidly converted to TMLA in aqueous solution, the results of this study reflect the genotoxicity of TMLA.
Remarks: In the dose range-finding study, toxicity, but no precipitation, was reported at concentrations of 1,000 ug/plate or more. TMA did not produce a positive mutagenic response under the conditions of this assay.
Reference: San and Wagner, 1991

(b)

Type: Mutagenicity
System of testing: *Salmonella* TA97, TA98, TA100, TA1535, TA1537
Concentration: 100; 333; 1,000; 3,333; 10,000 ug/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:
Cytotoxicity conc: 10,000 ug/plate
Precipitation conc: --
Genotoxic effects:

	+	?	--
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: Ames assay
GLP: Yes [ ] No [ ] ? [X]
Test substance: TMA. Because TMA is rapidly converted to TMLA in aqueous solution, the results of this study reflect the genotoxicity of TMLA.

Remarks: TMA was not mutagenic under the conditions of this assay
Reference: Mortelmans *et al.*, 1986

B. NON-BACTERIAL IN VITRO TEST

(a)
Type: HGPRT mutations
System of testing: Chinese hamster ovary cells
Concentration: 500; 750; 1,000; 1,500; 2,000 ug/mL
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

Results:
Cytotoxicity conc: --
Precipitation conc: --
Genotoxic effects:

	+	?	--
Without metabolic activation:	[ ]	[ ]	[X]

Method: OECD 476
GLP: Yes [X] No [ ] ? [ ]
Test substance: TMA dissolved in dimethylsulfoxide. Because TMA is rapidly converted to TMLA in aqueous solution, the results of this study reflect the genotoxicity of TMLA.
Remarks: The mutagenicity of TMA was evaluated using the CHO/HGPRT assay with and without liver S-9 from Aroclor induced rats. Results were negative under the conditions of this assay.
Reference: Bigger and Sigler, 1991

(b)
Type: Chromosomal aberrations
System of testing: Chinese hamster ovary cells
Concentration: 260, 520, 1040, 2080 ug/mL
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:
Cytotoxicity conc: Mitotic inhibition (41%) at highest concentration w/o activation
Precipitation conc: --
Genotoxic effects:

	+	?	--
Without metabolic activation:	[ ]	[ ]	[X]

Method: OECD 473
GLP: Yes [X] No [ ] ? [ ]
Test substance: TMA dissolved in dimethylsulfoxide. Because TMA is rapidly converted to TMLA in aqueous solution, the results of this study reflect the genotoxicity of TMLA.
Remarks: The cytogenicity of TMA was evaluated using the CHO cells with and without liver S-9 from Aroclor induced rats. Toxicity, as indicated by mitotic inhibition, was

noted at the highest concentration without activation. Results for chromosomal aberrations were negative under the conditions of this assay.

Reference: Putman and Morris, 1991

5.6 GENETIC TOXICITY IN VIVO

Although no in vivo genotoxicity studies were located for TMA or TMLA, the consistent negative results observed for these chemicals from in vitro studies suggests that the potential for significant genotoxicity is low.

5.7 CARCINOGENICITY

No data available

5.8 TOXICITY TO REPRODUCTION

Although a multigenerational reproductive toxicity test was not located for TMA or TMLA, data available from other studies suggest that the potential for significant toxicity to reproduction from exposures to these chemicals is low. For example, subchronic inhalation exposures of male and female rats to TMA concentrations up to 0.054 mg/m^3, or to TMLA concentrations up to 0.30 mg/m^3 did not result in any histopathological effects to reproductive tissues (IITRI, 1988, 1989). Similarly, no histopathological effects of reproductive tissues were observed in rats exposed to concentrations as high as 10,000 ppm TMA in feed (approximately 500 mg/kg-day) for 90 days (IBT, 1970; Hill Top, 1969), or in dogs exposed to concentrations as high as 20,000 ppm TMA in feed (approximately 500 mg/kg-day) for 13 weeks (Hill Top, 1969). Additionally, reproductive performance was not affected in female rats and guinea pigs following exposure to TMA concentrations of 0.5 mg/m^3 on days 6 through 15 of gestation (Ryan, 1988). Because TMA is likely hydrolyzed to form TMLA in tissues, these studies also provide information about TMLA

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a)

Species/strain:	Rat/Sprague-Dawley
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration:	Inhalation
Duration of the test:	6 hrs/day
Exposure period:	gestation day 6-15
Frequency of treatment:	Daily

Doses: 0, 500 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL Maternal Toxicity: --
NOEL Fetotoxicity: --
NOEL Teratogenicity 500 ug/m^3
Results: Lung foci and TMA-specific antibody were observed in exposed dams. TMA-specific antibody was also noted in neonatal rats. Lung foci were only observed in the challenged offspring whose mothers had not completely recovered from the original TMA exposure. Lung foci were not observed in adult rat offspring.
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: TMA. Because TMA is rapidly converted to TMLA in tissues, the results of this study reflect the developmental toxicity of TMLA.
Remarks: No teratogenic effects or fetal deaths were observed.
Reference: Ryan, 1988

(b)
Species/strain: Guinea Pig/Hartley
Sex: Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration: Inhalation
Duration of the test: 6 hrs/day
Exposure period: gd 6-15
Frequency of treatment: Daily
Doses: 0, 500 ug/m^3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL Maternal Toxicity: --
NOEL Fetotoxicity: 500 ug/m^3
NOEL Teratogenicity 500 ug/m^3
Results: Lung foci and TMA-specific antibody were observed in exposed dams. TMA-specific antibody was also noted in serum of guinea pig fetuses, but not in neonatal guinea pigs. Unlike rats (see separate summary above), lung foci were not observed in neonatal or adult guinea pigs.
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: TMA. Because TMA is rapidly converted to TMLA in tissues, the results of this study reflect the developmental toxicity of TMLA.
Remarks: No teratogenic effects or fetal deaths were observed.
Reference: Ryan, 1988

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

No data available

B. Toxicodynamics, toxicokinetics

(a)

Type:	Distribution and Kinetic Study
Species/Strain	Rat/Sprague-Dawley
Results:	T_{max} = <3 hours Elimination rate constants ranged from 0.015 – 0.214 Biological half-lives ranged from 3-46 days
Remarks:	Fourteen male and 14 female Sprague-Dawley rats were exposed to 950 ug/m^3 ^{14}C-radiolabeled TMA via inhalation for 45 minutes. Animals were sacrificed 3 hrs, 1, 2, 4, 8, 16, and 32 days post-exposure for tissue analysis. The highest concentrations were generally observed at the first time point (T_{max}<3 hours). A second T_{max} of eight-days was reported for lung lymph nodes in male rats, suggesting a potential role in gender lung toxicity in male rats as reported in a previous study. Sex differences in half-lives were reported for popliteal and lung lymph nodes, bone marrow, and heart. Because TMA is rapidly converted to TMLA in tissues, these data reflect TMLA kinetics as well.
References:	IITRI, 1988a

5.11 EXPERIENCE WITH HUMAN EXPOSURE

No data available.

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Robust Study Summaries for Trimellitic Acid

PHYSICAL/CHEMICAL ELEMENTS

MELTING POINT

TEST SUBSTANCE
- Trimellitic Acid (TMLA)

METHOD
- Method/guideline:
- GLP: ?
- Year (study performed):
- Remarks:

RESULTS
- Melting point: 219°C
- Decomposition:
- Sublimation:
- Remarks:

CONCLUSIONS
- The melting point for TMLA is 219°C

DATA QUALITY

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OTHER

- Melting point – 231°C. Chemfinder. 2001. http://chemfinder.camsoft.com

BOILING POINT

TEST SUBSTANCE

- Trimellitic Anhydride (TMA), a structurally similar chemical that rapidly hydrolyzes to
  TMLA in aqueous solution.

METHOD

- Method:
- GLP:
- Year (study performed):
- Remarks:

RESULTS

- Boiling point: 390°C (730°F)
- Pressure:
- Pressure unit:
- Decomposition (yes/no/ambiguous)-
  Remarks: Upon heating, trimellitic acid is converted to trimellitic anhydride prior to reaching the boiling point.

CONCLUSIONS

- The boiling point for TMA is 390 °C

DATA QUALITY

REFERENCES

- Amoco Corporation. 1997. Material Safety Data Sheet (www.vetmed.ucdavis.edu/msds/mf/Amoco/files/01260000.html)

OTHER

VAPOR PRESSURE

TEST SUBSTANCE
- Trimellitic Acid (TMLA)
- Remarks:

METHOD
- Method: estimated
- GLP: ?
- Year (study performed): 1985
- Remarks:

RESULTS
- Vapor Pressure: 3.8×10^{-6} Pa (2.88×10^{-8} mm Hg)
- Temperature: 25^{o}C
- Decomposition:
- Remarks:

CONCLUSIONS
- The vapor pressure for TMLA is 3.8×10^{-6} Pa.

DATA QUALITY

REFERENCES
- Neely, W.B. and Blaue, G.E. 1985. As cited in SRC PhysProp Database. 2001. http://esc.syrres.com/interkow/webprop.exe?CAS=528-44-9.

OTHER

PARTITION COEFFICIENT

TEST SUBSTANCE
- Trimellitic Acid (TMLA)

METHOD
- Method: calculated
- GLP: No
- Year (study performed): 2002
- Remarks: Used SMILES notation of O=C(O)c(ccc(c1C(=O)O)C(=O)O)c1

RESULTS
- Log Pow: 0.95
- Temperature: 25º C
- Remarks: Calculated using QSAR software KOWWIN

CONCLUSIONS
- The Log P_{ow} value for TMLA is 0.95

DATA QUALITY
- Klimisch Code = 2 Reliable with restrictions. Value is an estimate by an accepted method.

REFERENCES
- KOWWIN Version 1.66. 2000.(http://www.epa.gov/oppt/exposure/docs/episuitedl.htm).

OTHER
- Estimated Log P_{ow}: 0.57. CLOGP Program (http://www.daylight.com)
- Estimated Log P_{ow}: 0.81 Interactive Analysis Program (http://www.logp.com
- Estimated Log P_{ow}: 0.78 ALOGP Program (http://www.lhn.unil.ch/Appl/cchem2.html)
- Estimated Log P_{ow}: 0.87 XLOGP Program (ftp2.ipc.pku.edu.cn)

WATER SOLUBILITY

TEST SUBSTANCE
- Identity: Trimellitic Acid (TMLA)
- Remarks:

METHOD
- Method:
- GLP: ?
- Year (study performed):
- Remarks:

RESULTS
- Value: 21,000 mg/L
- Description of solubility:
- pH value and concentration at temperature °C:
- pKa value at 25 °C:
- Remarks: Moderate solubility.

CONCLUSIONS
- TMLA has moderate solubility in water.

DATA QUALITY

REFERENCES
- Experimental water solubility – 2.1×10^4 mg/l at 25°C. Bemis, A.G. et al. 1982. As cited in SRC PhysProp Database. 2001. http://esc.syrres.com/interkow/webprop.exe?CAS=528-44-9. Amoco Corporation. 1997. Material Safety Data Sheet (www.vetmed.ucdavis.edu/msds/mf/Amoco/files/01260000.html)
- Trimellitic anhydride fact sheet, http://ull.chemistry.uadron.edu/erd/chemicals/2501- 3000/2996.html

OTHER

ENVIRONMENTAL FATE ELEMENTS AND PATHWAYS

PHOTODEGRADATION

TEST SUBSTANCE
- Trimellitic Acid (TMLA)

METHOD
- Method/guideline: Estimated - AOPWIN
- Type (test type): Estimated
- GLP:
- Year (study performed): 2001
- The atmospheric hydroxyl radical concentration of 1.5 x 10^6 molecule/cm^3 was used as a standard default in the program.

RESULTS
- Direct photolysis:
- Half-life t ½ : 6.55 days
- Remarks: Overall OH Rate Constant: 1.6E-12 cm^3/molecule-sec

CONCLUSIONS

DATA QUALITY
- Reliability: Klimisch Code= 2 Reliable with restrictions. The value derived is an estimate using accepted methods.

REFERENCES
- SRC. 2001. Atmospheric Oxidation Program for Microsoft Windows (AOPWIN). Syracuse Research Center.

OTHER

STABILITY IN WATER

TEST SUBSTANCE
- Trimellitic Acid (TMLA)

METHOD
- Method/guideline:
- Type (test type):
- GLP:
- Year (study performed):
- Remarks: Based on the chemical structure, trimellitic acid is not expected to undergo abiotic hydrolysis in the environment.
- Duration:
- Positive Controls:
- Negative Controls:
- Analytical procedures:

RESULTS
- Measured value:
- Degradation: Breakdown products: .
- Remarks:

CONCLUSIONS
- Based on the chemical structure, trimellitic acid is not expected to undergo abiotic hydrolysis in the environment

DATA QUALITY

REFERENCES

OTHER

TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

TEST SUBSTANCE
- Trimellitic Acid (TMLA)
- Remarks:

METHOD
- Test (test type): Calculated
- Method: Levels I, II, and III
- Year (study performed): 2002
- Remarks:
- Chemical Assumptions: Molecular weight – 210, water solubility – 21,000 g/m^3; vapor pressure – 3.84×10^{-6} Pa; Log P_{ow} – 0.95; melting point – 219 ^oC; half-life in air – 157.2 hours; half-life in water – 360 hours; half-life in soil – 360 hours; half-life in sediment – 1440 hours; all other parameters were default values. Level III model assumed continuous 1000 kg/hr releases to each compartment (air, water, soil).

RESULTS
- Media: At equilibrium, most TMLA is expected to be in water. Lesser concentrations might occur in soil and sediment. Virtually npo TMLA will partition to air. Air, soil, water, and sediment concentrations were estimated.
- Estimated Distribution and Media Concentration:

	Level I	**Level II**	**Level III**
Air	7.68E-7%	7.68E-7%	3.46E-6%
Water	99.2%	99.2%	50.6%
Soil	0.78%	0.78%	49.3%
Sediment	0.02%	0.02%	0.02%

- Remarks: Since default assumptions for release estimates were used, resulting environmental concentrations are not provided.

CONCLUSIONS
- TMLA will partition to water. Virtually no TMLA will partition to air. Soil and sediment concentrations will be minimal at equilibrium. The Level III model suggests soil may contain s significant percentage of TMLA, reflecting the assumed pattern of chemical release (equal loading of water, soil and air).

DATA QUALITY
- Reliability: Klimisch Code= 2 Reliable with restrictions. The value derived is an estimate using accepted methods.

REFERENCES

- Trent University. 1991. Fugacity-based Environmental Equilibrium Partitioning Model. Version 2.17. Environmental Modeling Centre, Trent University, Peterborough, Ontario. (available at http://www.trentu.ca/envmodel)

OTHER

BIODEGRADATION

TEST SUBSTANCE
- Trimellitic Anhydride (TMA)
- Purity 98% with the majority of the remaining material being trimellitic acid.

METHOD
- Method/guideline: OECD 301B
- Test Type: Modified Sturm-Test
- GLP: Yes
- Year (study performed): 1991
- Contact time (units): 30 days
- Innoculum: sewage microorganisms
- Remarks field for Test Conditions: Two concentrations were tested: 10.19 and 20.29 mg/L TMA.

RESULTS
- Degradation % after time: For 10 mg/L TMA system, 975 of the theoretical CO_2 ($ThCO_2$) was generated within 28 days. For the 20 mg/L TMA system, 77% of the $ThCO_2$ was generated within 28 days.
- For each time period %: For the 10 mg/L TMA system: Day 5 – 65% $ThCO_2$, Day 12 – 89% $ThCO_2$, Day 20 – 96% $ThCO_2$ and Day 30 – 99% $ThCO_2$. For the 20 mg/L TMA system: Day 5 – 57% $ThCO_2$, Day 12 – 72% $ThCO_2$, and Day 20 – 76% $ThCO_2$, and Day 30 – 77% $ThCO_2$.
- Breakdown products: Carbon dioxide was measured.
- Remarks field for Results: TMA was degraded upon action of microorganisms under aerobic conditions. The biodegradation rates in the different concentrations were not the same. However, the criteria for "readily biodegradable" were achieved in both concentrations. Given the rapid hydrolysis of TMA to TMLA, results most likely reflect biodegradation of TMLA.

CONCLUSIONS
- TMLA is readily biodegradable.

DATA QUALITY
- Reliability: Klimisch Code= 1

REFERENCES
- Battelle Europe. 1991. Study on the Ready Biodegradability (modified Sturm Test) of Trimellitic Anhydride. Study-No: BE-EA-128-91-01-STT-01.

OTHER

ECOTOXICITY ELEMENTS

ACUTE TOXICITY TO FISH

TEST SUBSTANCE
- Trimellitic Acid (TMLA)
- Remarks: 98% pure TMA

METHOD
- Method/guideline: OECD 203 and according to "German Water Endangerment Classification Scheme, DIN 38 412, Part 15".
- Type (test type): Acute toxicity to fish
- GLP: Yes
- Year (study performed): 1991
- Species/Strain/Supplier: *Leuciscus idus melanotus* (Golden orfe)
- Analytical monitoring: High performance thin-layer chromatography (HPTLC)
- Exposure period (unit): 96 hours
- Statistical methods: Probit Analysis
- Details of test: flow-through test system and static
- Remarks: It is thought that TMA was hydrolyzed under test conditions. As a result, it is believed that under test conditions and after pH adjustment to the required physiological value, TMLA and Trimellitic Sodium Salt (TSS), respectively, were the test materials investigated in this study.

RESULTS
- Nominal concentrations: 130, 220, 350, 600, and 1,000 mg/L
- Measured concentrations: 70-129% (average of 95.8%)
- Element value: Based on nominal concentrations: LC_0=>1,000 mg/L; LC_{50}=could not be determined; NOEC=> = 1,000 mg/L. Based on measured average concentrations: LC_0=896 mg/L.
- Statistical results: descriptive
- Remarks:

CONCLUSIONS
- TMLA has low toxicity to *Leuciscus idus melanotus.*

DATA QUALITY
- Reliability: Klimisch Code= 1

REFERENCES
- Battelle Europe. 1993. A Study of the Acute Toxicity to Fish (*Leuciscus idus melanotus*) of Trimellitic Anhydride. Study Number: BE-EA-128-91-01-F3A-1.

OTHER

TOXICITY TO AQUATIC PLANTS (*e.g.*., ALGAE)

TEST SUBSTANCE
- Trimellitic Acid (TMLA)
- Remarks: 98% pure TMA

METHOD
- Method/guideline: OECD 201
- Test type (static/other): static
- GLP: Yes
- Year (study performed): 1992
- Species/strain # and source: *Scenedesmus subspicatus* (Chodat, SAG 86.81); green algae.
- Element basis: THOMA Counting Chamber with Microscop Metalux II.
- Exposure period, date of start and end of the test [Duration]: 96 hours
- Analytical monitoring: High performance thin-layer chromatography apparatus (HPTLC)
- Statistical methods: One-way Analysis of Variance (ANOVA) with Bonferroni multiple range test
- Remarks: Average initial cell density was 10^4 cells/mL; Temperature = 23 C; pH = 8.3. It is thought that TMA was hydrolysed under test conditions. As a result it is believed that under test conditions and after pH adjustment to the required physiological value TMLA and Trimellitic Sodium Salt (TSS), respectively, were the test materials investigated in this study.

RESULTS
- Nominal concentrations: 62.5, 125, 250, 500, and 1,000 mg/L
- Measured concentrations: 73-110% (average of 86.8%)
- Unit:
- Element value: After a 96 hour exposure, analyzed concentrations of the test material were relatively unchanged from measurements at 0 hours.
- NOEC, LOEC, or NOEL, LOEL: Based on nominal concentrations: NOEC>=1,000 mg/L; Based on measured average concentrations: NOEC >= 739 mg/L.
  Was control response satisfactory: Yes
- Statistical results: descriptive.
- Remarks:

CONCLUSIONS
- TMLA has low toxicity to *Scenedesmus subspicatus.*

DATA QUALITY
- Reliability: Klimisch Code = 1.

REFERENCES

- Knacker et al., 1993. A Study of the Toxcity to Algae (*Scenedesmus subspicatus*) of Trimellitic Anhydride. Study Number: BE-EA-128-91-02-ALG-1.

OTHER

ACUTE TOXICITY TO AQUATIC INVERTEBRATES (*e.g.*, DAPHNIA)

TEST SUBSTANCE
- Trimellitic Acid (TMLA)
- Remarks: 98% pure TMA

METHOD
- Method/guideline: OECD 202, Part I
- Test type: Acute toxicity test
- GLP: Yes
- Year (study performed): 1991
- Species/Strain: *Daphnia magna* (Straus), water-flea
- Test details: static
- Statistical methods: Probit analysis. When less than three test substance concentrations caused immobilization between 0% and 100% the geometrical mean was used to determine the EC_{50}.
- Exposure period: 48 hours-
- Remarks: It is thought that TMA was hydrolyzed under test conditions. As a result it is believed that under test conditions and after pH adjustment to the required physiological value, TMLA and Trimellitic Sodium Salt, respectively, were the test materials investigated in this study.

RESULTS
- Nominal concentrations: 130, 220, 350, 600, and 1,000 mg/L
- Measured concentrations: 21-82% (average of 52.5%)
- Unit:
- EC50, EL50, LC0, LL0, at 48 hours: Based on nominal concentrations: EC_0=1,000 mg/L, EC_{50}=could not be determined, NOEC=> = 1,000 mg/L. Based on measured average concentration: EC_0=>792 mg/L
- Statistical results: descriptive
- Remarks:

CONCLUSIONS
- TMLA has low toxicity to *Daphnia magna*.

DATA QUALITY
- Reliability: Klimisch Code=1

REFERENCES
- Knacker *et al.*, 1992. A Study of the Acute Immobilisation to *Daphnia* of Trimellitic Anhydride. Study Number: BE-EA-128-91-02-DAK-1.

OTHER

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE
- Trimellitic Acid (TMLA)

METHOD
- Method/guideline: Acute inhalation toxicity
- Type (test type): lethality study
- GLP: Yes
- Year (study performed): 1988
- Species/Strain: Sprague-Dawley Rats
- Sex: male/female
- No. of animals per sex per dose: five male and five females at each dose.
- Vehicle:
- Route of administration: inhalation
- Remarks: The rats were exposed to an uncorrected particulate aerosol concentration of 6,010 mg/m^3. The average particle size of the chamber atmosphere was 7.70 microns with 37.5% of the particles measuring over 10 microns. Therefore, the rats were exposed to a respirable concentration of 3,750 mg/m^3.

RESULTS
- LC_{50} Value: >3,750 mg/m^3.
- Number of deaths at each dose level: 0 at all levels.
- Remarks: Clinical signs observed immediately following the exposure were minimal and mostly due to confinement in the nose-only exposure tubes. The rats appeared normal within two days following the exposure and for the duration of the study. All rats gained weight during the study. Gross pathology reveled five rats with no gross lesions, three with lung foci, two withred area on the lungs and one with a distended bladder. These findings were considered of a minor nature and within normal limits.

CONCLUSIONS
- The acute inhalation LC_{50} of TMLA is >3,750 mg/m^3.

DATA QUALITY
- Reliability: Klimisch Code=1

REFERENCES
- IITRI. 1988. Acute Inhalation Toxicity Study of Trimellitic Acid in Rats. IITRI Project No. L08100, Study No. 1423.

OTHER

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE
- Trimellitic acid (TMLA)
- Remarks: 98.0 % pure

METHOD
- Method/guideline: Abbreviated Primary Eye Irritation
- Type (test type): Eye irritation
- GLP: No
- Year (study performed): 1988
- Species/Strain: New Zealand Albino rabbit
- Sex: no specified
- No. of animals per sex per dose: Not specified
- Vehicle: none
- Concentrations: 0.1 grams of undiluted TMLA
- Remarks: TMLA was administered undiluted at a dose of 0.1 grams into one eye of each of three rabbits with the other eye serving as the untreated control. The treated eye was scored for irritation at 1, 24, 48 and 72 hours and at 7, 14 and 21 days following test article administration. Irritation was scored using the Draize method. A reaction was considered positive if at any observation period, the test article produced ulceration or opacity of the cornea (cornea score > than 0), inflammation or slight circumcorneal injection of blood vessels of the iris (iris score > 0), any obvious conjunctival swelling with partial eversion of the lids (chemosis score 2 or greater), or conjunctival erythema of diffuse crimson red (erythema score 2 or greater) with individual vessels not easily discernable

RESULTS
- The maximum eye irritation score of 59.7/110 was obtained 24 hours after administration of the test article. Lackluster pitting and pannus formation were also observed during the study

CONCLUSIONS
- TMLA is severely irritating to eyes.

DATA QUALITY Reliability:
Klimisch Code= 2 (individual animal data were not available)

REMARK

REFERENCES
- IIT Research Institute. 1991. Primary Eye Irritation Study of TMA in Rabbits. Study No. 1693

OTHER

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE
- Trimellitic acid (TMLA)
- Remarks: 98.0 % pure

METHOD
- Method/guideline: Abbreviated Acute Dermal Irritancy/Corrosivity Study
- Type (test type): skin irritation
- GLP: No
- Year (study performed): 1988
- Species/Strain: New Zealand White rabbit
- Sex: not specified
- No. of animals per sex per dose: Not specified
- Vehicle: none
- Concentrations: 0.5 grams of undiluted TMA
- Remarks: TMLA was administered undiluted at a dose of 0.5 grams to the shaved backs of three rabbits. The application site was covered with an adhesive dressing. After 4 hours the dressings were removed and residual test article was rinsed from the application. The skin of the animal was scored for irritation at 30-60 minutes, 24, 48, and 72 hours and 7 and 14 days following removal of the wrappings. Skin reactions were graded according to the Draize method.

RESULTS
- The dermal irritation score ranged from 0.7 at 30-60 minutes following unwrapping to 0.0/8.0 at 48 and 72 hours. The primary dermal irritation score (PDIS) for trimellitic anhydride was 0.2 (erythema/eschar formation + edema at 24 hours)+ (erythema/eschar formation + edema at 72 hours)/ 2 = PDIS

CONCLUSIONS
- TMLA is a mild skin irritant.

DATA QUALITY Reliability:
Klimisch Code= 2 (individual animal scores were not included)

REMARK.

REFERENCES
- IIT Research Institute. 1991. Acute Dermal Irritancy/Corrosivity Study of Trimellitic Anhydride in Rabbits. Study No. 1694

OTHER

GENETIC TOXICITY ELEMENTS

GENETIC TOXICITY IN VITRO (CHROMOSOMAL ABERRATIONS)

TEST SUBSTANCE
- Trimellitic Acid (TMLA)
- Remarks - It is thought that TMA was hydrolyzed under test conditions. As a result it is believed that under test conditions and after pH adjustment to the required physiological value, TMLA and Trimellitic Sodium Salt were the test materials investigated in this study.

METHOD
- Method/guideline: Chromosomal Aberrations in Chinese Hamster Ovary Cells (CHO) with Confirmation (Evans, 1976; Preston *et al*., 1981) (OECD 473)
- Type (test type): mammalian cell aberration assay
- GLP: Yes
- Year (study performed): 1991
- Cells: Chinese Hamster Ovary
- Concentration levels: 260, 520, 1,040, and 2,080 mg/L
- Exposure period: 14 hours (non activated study), 12 hours (S-9 activation study)
- Statistical methods: Fisher's exact test
- Remarks: Dose selection was limited by the insolubility of TMA in solvent at concentrations exceeding 2,080 mg/L.
- Control groups: triethylenemlamine (TEM), cyclophosphamide (CP), dimethylsulfoxide (DMSO)
- Criteria for evaluating results: Toxicity measured by mitotic inhibition.

RESULTS
- Chromosomal Aberrations
- With metabolic activation: negative
- Without metabolic activation: negative

CONCLUSIONS
- TMA was concluded to be negative in the CHO cytogenics assay

DATA QUALITY
- Reliability: Klimisch Code=1

REFERENCES
- Putnam and Morris. 1991. Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. Microbiological Associates, Inc. Laboratory Study Number: TA039.337100

OTHER

GENETIC TOXICITY IN VITRO (HGPRT Mutation Assays)

TEST SUBSTANCE
- Trimellitic Acid (TMLA)
- Remarks: It is believed that TMA is rapidly hydrolyzed to the acid (TMLA) under test conditions. Therefore, TMLA is actually being tested in this assay.

METHOD
- Method/guideline: CHO/HGPRT Mutation Assay with Confirmation
- Type (test type): Mutation assay
- GLP: Yes
- Year (study performed): 1991
- Cells: Chinese Hamster Ovary
- Concentration levels: 500, 750, 1,000, 1,500, 2,000 mg/L
- Exposure period: 5 hours
- Statistical methods: Descriptive
- Remarks: Dose levels were selected following a preliminary toxicity test.
- Control groups: ethyl methanesulfonate, benzo(a)pyrene, dimethylsulfoxide (DMSO)
- Criteria for evaluating results: Assay considered positive in the event of a dose-dependant increase in mutant frequencies with at least two consecutive doses showing mutant frequencies that are elevated above 40 mutants per 10^6 clonable cells.

RESULTS
- Genotoxic effects;
- With metabolic activation: negative
- Without metabolic activation: negative

CONCLUSIONS
- Under the conditions of this report, TMA was found to be negative in both the absence and presence of exogenous metabolic activation. Since TMLA is rapidly formed from the hydrolysis of TMA, TMLA was likely testes as a consequence of this hydrolysis in this test system.

DATA QUALITY
- Reliability: Klimisch Code=1

REFERENCES
- Bigger and Sigler. 1991. CHO/HGPRT Mutation Assay with Confirmation. Microbiological Associates, Inc. Laboratory Study Number: TA039.332001

OTHER

GENETIC TOXICITY *IN VITRO* (GENE MUTATIONS)

TEST SUBSTANCE

- Trimellitic acid (TMLA)
- Remarks: It is believed that TMA is rapidly hydrolyzed to the acid (TMLA) under test conditions. Therefore, TMLA is actually being tested in this assay.

METHOD

- Method/guideline: Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay with a Confirmatory Assay
- Type: Mutation reversion assay
- System of testing: Bacterial
- GLP: Yes
- Year (study performed): 1991
- Cell line: *Salmonella typhimurium* TA98, TA1535, TA1537, TA1538, TA100.
- Metabolic activation: Liver S-9, Aroclor-induced
- Species: Rat
- Concentrations tested: 0, 33, 100, 333, 1,000, 3,333, 10,000 µg/plate
- Statistical Methods:
- Number of replicates: 3
- Positive and negative control groups and treatment: 2-aminofluorene, 9-aminoacridine, sodium azide, 2-nitrofluorene, dimethylsulfoxide (DMSO)
- Criteria for evaluating results (*e.g.* cell evaluated per dose group): For the test article to be positive, it must cause a dose-related increase in the mean revertants per plate of at least one tester strain with a minimum of two increasing concentrations of test article.

RESULTS

- Genotoxic effects
- With metabolic activation: negative
- Without metabolic activation: negative

CONCLUSIONS

- TMA did not cause a positive response in the Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay with a Confirmatory Assay. Since TMA is rapidly hydrolyzed to TMLA, it is assumed that TMLA was actually tested under the conditions of this assay.

DATA QUALITY

Reliability: Klimisch Code= 1

REFERENCES

- San and Wagner. 1991. Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay. Microbiological Associates, Inc. Laboratory Study Number TA039.501014.

OTHER

REPEATED DOSE TOXICITY

TEST SUBSTANCE
- Trimellitic Acid (TMLA)

METHOD
- Method/guideline followed: Thirteen-week inhalation toxicity study
- Test type: Subchronic inhalation toxicity test
- GLP (Y/N): ?
- Year (study performed): 1989
- Species: Rat Strain: Sprague-Dawley
- Route of administration: inhalation
- Duration of test: 13 weeks
- Doses/concentration levels: 0, 0.050, 0.10, or 0.30 mg/m^3
- Sex: male & female
- Exposure period: 13 weeks
- Frequency of treatment: 6 hours/day; 5 days/week
- Control group and treatment: clean filtered air
- Post exposure observation period: 4 weeks
- Statistical methods: ANOVA
- Test Subjects
- Age at study initiation: 8 weeks
- No. of animals per sex per dose: 20 (0 mg/m^3); 20 (0.050 mg/m^3); 20 (0.10 mg/m^3); and 30 (0.30 mg/m^3).
- Study Design
- Vehicle: clean filtered air
- Clinical observations performed and frequency: 1x/day
- Organs examined at necropsy: Adrenals, brain, epididymis, eyes, esophagus, femur and bone marrow (smear), gonads, heart, douodenum, jejunum, ileum, cecum, colon, kidneys, liver, lungs, lymph nodes (mandibular, respiratory, and mesenteric), mammary gland, nasal turbinates, pancreas, prathyroids, pituitary, prostate and seminal vesicles, salivary glands, sciatic nerve, skeletal muscle, skin, spinal cord, spleen, sternum, stomach, thymus, thyroids, tongue, trachea, urinary bladder, uterus, and ear with attached tag.

RESULTS
- NOAEL (NOEL): 0.30 mg/m^3
- Remarks field for Results: No mortalities were noted in any of the test groups. Gross necropsy findings among 13-week exposed and 4-week recovered rats included small numbers of external lung foci and discolored areas on and/or enlarged mandibular lymph nodes, but these occurred among controls as frequently as among test article-exposed groups.

CONCLUSIONS
- No systemic toxicity was noted in this thirteen-week inhalation study. In addition, no mortalities occurred in any of the test groups.

REFERENCES

- IITRI. 1989. Thirteen-week Inhalation Toxicity Study of Trimellitic Acid (TMLA) in Rats. Project No. L8100, Study No. 1424.

OTHER

TOXICITY TO REPRODUCTION

TEST SUBSTANCE

- TMLA
- Remarks: It is believed that TMA is rapidly hydrolyzed to the acid (TMLA) within tissues following exposure to TMA. Therefore, TMLA is actually being tested in this assay.

METHOD

- Method/guideline followed: ?
- Test type: Subchronic oral toxicity test
- GLP (Y/N): ?
- Year (study performed): 1970
- Species: Rat
- Strain: albino
- Route of administration: feed
- Duration of test: 90 days
- Doses/concentration levels: 0, 10,000 ppm
- Sex: male & female
- Exposure period: 90 days
- Frequency of treatment: daily
- Test Subjects
- Age at study initiation: not specified
- No. of animals per sex per dose: 10 male, 10 female / per dose
- Study Design
- Vehicle: feed
- Clinical observations performed and frequency: weekly
- Organs examined at necropsy: Histopathological analysis included the following reproductive tissues: ovary, testes, seminal vesicle

RESULTS

- 10,000 ppm in feed was identified as a NOAEL. Assuming a default feed intake of 0.05 kg feed/kg body weight per day, this feed concentration corresponds to a dose of approximately 500 mg/kg-day.

CONCLUSIONS

- TMLA does not produce histopathological effects in reproductive tissues following subchronic oral exposures to high doses.

DATA QUALITY

REFERENCES

- Industrial Bio-Test Laboratories. 1970. Report to standard oil company (Indiana): Ninety-day subacute oral toxicity of LM 3813 in albino rats. IBT B7989.

- Hill Top Research. 1969. Thirteen week dietary administration of trimellitic anhydride to rats. S-192.
- Hill Top Research. 1969. Dietary administration of trimellitic anhydride to dogs for 13 weeks. S-260.

OTHER

- Although a multigenerational reproductive toxicity test was not located for TMLA, data available from other studies suggest that the potential for significant toxicity to reproduction from TMLA exposures is low.

- Subchronic inhalation exposures of male and female rats to TMA concentrations of 0.002, 0.015, or 0.054 mg/m^3 did not result in any histopathological effects to reproductive tissues (IITRI, 1988). Additionally, reproductive performance was not affected in female rats and guinea pigs following exposure to TMA concentrations of 0.5 mg/m^3 on days 6 through 15 of gestation (Ryan, 1988).
  Oral exposures to TMA in the diet at concentrations of 1,000, 10,000 or 20,000 ppm for 13 weeks did not produce any histopathological effects in the reproductive tissues (gonads) of male and female beagle dogs (4 per dose level) (Hill Top Research, 1969). Assuming a default feed intake of 0.025 kg feed/kg bodyweight per day, the highest concentration corresponds to a dose of approximately 500 mg/kg-day.
  Oral exposures to TMA in the diet at concentrations of 1,000, 5,000 or 10,000 ppm for 13 weeks did not produce any histopathological effects in the reproductive tissues (gonad, uterus) of male and female rats (20 per dose level) (Hill Top Research, 1969). Assuming a default feed intake of 0.05 kg feed/kg bodyweight per day, the highest concentration corresponds to a dose of approximately 500 mg/kg-day.

DEVELOPMENTAL TOXICITY/TERATOGENICITY

TEST SUBSTANCE

- Trimellitic Acid (TMLA)
- Remarks: It is believed that TMA is rapidly hydrolyzed to the acid (TMLA) within tissues following exposure to TMA. Therefore, TMLA is actually being tested in this assay.

METHOD

- Method/guideline: Teratological Evaluation - Inhalation
- GLP: ?
- Year (study performed): 1988
- Species: Rat, Guinea Pig
- Strain: Sprague-Dawley (rat), Hartley (guinea pig)
- Route of administration: inhalation
- Doses/concentration levels: 0 and 500 ug/m^3
- Sex: Female
- Exposure period: Gestation days 6-15 (rats), 6-26 (guinea pigs)
- Frequency of treatment: Daily
- Control group and treatment: filtered air
- Duration of test: 6 hours/day
- Statistical methods: t-test, ANOVA
- Remarks:

RESULTS

- Maternal toxicity: No significant effects were detected in gravid uterus weights or in body weights for either species.
- Developmental toxicity: No significant differences in body weights were detected between the fetuses in the treated and control groups. No significant variations or malformations were observed in the gross external appearance, viscera, skeletal system, or development of the brain in either species.

CONCLUSIONS

- No treatment-related effects were observed in maternal, fetal, or offspring body weights, or litter viability in either species. No teratogenic effects were observed in either species.

DATA QUALITY

REFERENCES

- Ryan, B.M. 1988. Teratological Evaluation of Trimellitic Anhydride (TMA) in Rats and Guinea Pigs. Submitted in partial fulfillment of the requirements for the degree of Master of Science in Biology in the School of Advanced Studies of Illinois Institute of Technology.

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