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Toxicology & Product Regulatory
Compliance Department
5 Garret Mountain Plaza
West Paterson, NJ 07424

Phone 973 357- 3372
Fax 973 357-3057
Email: Randy_Deskin@gm.Cytec.com

September 19, 2002

Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
PO Box 1473
Merrifield, VA 22116
ATTN: Chemical Right-To-Know Program

Dear Administrator Whitman:

In keeping with Cytec's 1999 commitment to the EPA High Production Volume Voluntary program, attached find a robust summary and test plan for CAS # 2778-42-9, Isocyanic acid, m-phenylenediiso-propylidene.

The robust summary and test plan is provided as hard copy and in pdf format.

Sincerely,

Randy Deskin, Ph.D., DABT
Director, Toxicology and Product Regulatory Compliance Department

AR201-13996A

High Production Volume (HPV) Challenge Program

Data Summary and Test Plan
for

TMXDI® (META) ALIPHATIC ISOCYANATE

Isocyanic acid, m-phenylenediiso-propylidene
CAS# 2778-42-9

Prepared by

Cytec Industries Inc.
5 Garret Mountain Plaza
West Paterson, NJ 07052

Date September 19, 2002

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A. INTRODUCTION

On November 22, 1999, Cytec Industries Inc. (Cytec) voluntarily agreed to participate in the Environmental Protection Agency's (EPA) High Production Volume Chemical Challenge Program. By participating in this program, Cytec agreed to assess the adequacy of existing data, design and submit test plans to fill data gaps where necessary and appropriate, provide test results, and prepare summaries of the data characterizing each chemical.

The sponsored chemical addressed in this test plan is Isocyanic acid, m-phenylenediiso-propylidene (CAS# 2778-42-9) (TMXDI).

B. GENERAL SUBSTANCE INFORMATION

Trade Name: TMXDI® (META) ALIPHATIC ISOCYANATE

Chemical Name: Isocyanic acid, m-phenylenediiso-propylidene

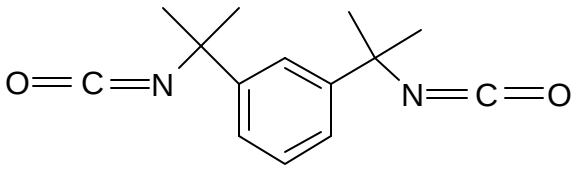
Inventory Names:
Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-
1,3-Bis(1-isocyanato-1-methylethyl)benzene
1,3-bis(1-isocyanato-1-methylethyl)benzene
1,3-Bis(1-isocyanato-1-methylethyl)benzol
1,3-bis(1-isocianato-1-metiletil)benceno

Other Names:
a,a,a',a'-Tetramethyl-m-phenylenedimethylene diisocyanate
a,a,a',a'-Tetramethyl-m-xylylene diisocyanate
1,3-Bis(a-isocyanatoisopropyl)benzene
Isocyanic acid, a,a,a',a'-tetramethyl-m-xylylene ester
Isocyanic acid, m-phenylenediisopropylidene ester
m-Bis(1-isocyanato-1-methylethyl)benzene
TMXDI
Tetramethyl-m-xylylene diisocyanate

Chemical Abstract Service Registry Number: CAS # 2778-42-9
Common Name: TMXDI

Empirical Formula: $C_{14}H_{16}N_2O_2$
Molecular Weight: 244.3

Structure:



C. EXPOSURE INFORMATION

1. Use and Exposure Information

Cytec Industries Inc. has produced in excess of 1 million pounds of this material, as reported on the 1990 IUR. There are prescribed conditions for its manufacture, processing, distribution, use and disposal. In general, there is low potential for exposure of humans or the environment. In the work place, potential worker exposure is carefully controlled.

2. Manufacture & Processing:

Although diisocyanates are well-known sensitizers, little risk is posed by this chemical. The diisocyanate is manufactured in a closed system with little personnel exposure. Its manufacture is monitored under close technical supervision. Although its vapor pressure is quite low, points of possible exposure are controlled by exhaust systems and, where necessary, carbon filters are used to purify any contaminated air. Protective clothing and respirators are required.

The only potential worker contact comes from sampling procedures for quality control, and in some instances, during packaging. Exposure would be by skin contact. Inhalation exposure is extremely low due to the use of ventilation and the materials low vapor pressure. Ingestion would not be expected.

In customer applications, this material is used at plants by trained personnel well equipped to handle these materials safely.

TMXDI is not sold directly to the consumer market. This material is reacted into the polymers in which they are added, limiting potential exposure in the finished consumer products. Residual levels are low in finished consumer products.

3. Distribution (Transport):

Since diisocyanates are well known sensitizers, distribution of this material is restricted to customers that are highly experienced and well equipped to handle material of this kind. Industry practice for plants handling isocyanates is to routinely use exhaust systems to minimize hazards due to contaminated air, and where required, protective clothing and respirators are used.

This material is transported to our customers in drums, totes, or ISO containers by way of truck or ship with little risk to the public or the environment. Emergency Response and Incident

Management processes are in place to minimize exposure to human health and the environment in the unlikely event of an accidental spill or release.

4. Uses:

TMXDI aliphatic isocyanate is a versatile aliphatic isocyanate finding broad end-use applicability. Application areas include specialty coatings, aqueous dispersions, automotive coatings, herbicide coatings, inks, sealants, adhesives, thermoplastic urethanes, and lacquers.

This chemical imparts improved physical properties to polyurethane products, affording higher strength and improved adhesion, appearance, and flexibility, resulting in more durable products. Common commercial products that may have been made using TMXDI include, fabric and leather finishes, adhesives, automotive paints, printing inks, sealants, and wood coatings. TMXDI poses little to no risk to the end consumer .

In addition to these uses, TMXDI is FDA approved for use in food-packaging under specific listings in the Code of Federal Regulations (CFR) Title 21-Food and Drugs Chapter I-Food and Drug Administration, Department of Health and Human Services.

Table 1: 21 CFR Sanctions

21 CFR	Section	Definition
PART 175—Indirect Food Additives: Adhesives and Components of Coatings--§175.105 (ADHESIVES)	§175.105	Clears meta-tetramethyl xylene diisocyanate for reaction with one or more of the polyols and polyesters listed in §175.105 and dimethylolpropionic acid and triethylamine, N-methyldiethanolamine, 2-dimethylaminoethanol, 2-dimethyl-amino-2-methyl-1-propanol and/or 2-amino-2-methyl-1-propanol in the production of polyurethane resins intended for use as components of adhesive formulations used in food packaging applications. Cytec Industries Petition Oct. 26, 1993, effective March 12, 1996

5. Disposal:

All waste material is drummed and disposed of by approved waste treatment contractors. This material is not regulated as a RCRA hazardous waste

D. SUMMARY TABLE OF AVAILABLE DATA

CAS# 2778-42-9	Study Date	Results	Data Accept-able
Physical/Chemical Characteristics			
Melting Point	1982	-10°C	Yes
Boiling Point	1982/ 2002	292 °C (105 °C @ 0.5 mm Hg) 320 °C (est.)	Yes
Vapor Pressure	1986/ 2002	0.0032 mm Hg @ 25 °C 0.00298 mm Hg @ 25 °C (est.)	Yes
Partition Coefficient	2002	Log K_{ow} = 4.74	Yes
Water Solubility	2002/ 2002	Insoluble (reacts with water) 5.833 mg/L @ 25 °C (est.)	Yes
Environmental Fate			
Photodegradation	2002	For reaction with hydroxyl radical, predicted rate constant = 10.1332×10^{-12} cm^3/molecule-sec Predicted half-life = 12.666 hours	Yes
Stability in Water	2002	No estimate available, Reacts slowly with water resulting in the formation of insoluble ureas.	Yes
Transport between Environmental Compartments: **Fugacity Level III Model** Default assumption: 1000 kg/hr simultaneously released into air, water, and soil.	2002	Air: 0.779% Water: 18.1% Soil: 62.6% Sediment: 18.5%	Yes
Biodegradation	1988	*OECD 301D: Closed Bottle Test* Not readily biodegradable by this test procedure	Yes
Ecotoxicity			
Acute Toxicity to Fish	1993	*OECD 203: Fish Acute Toxicity Test* Lepomis macrochirus: NOEC = >52.19 mg/L 96 hr LC50 = >65.88 mg/L (based on exposure to Water Accommodating Fraction, measured by analysis)	Yes
	1986	*USEPA 660/3-75-009: Fish Acute Toxicity Test* Pimephales promelas NOEC = 0.32 mg/L **96 hr LC50 = 0.67 mg/L** (based on material dissolved in acetone)	Yes

Acute Toxicity to Invertebrates	1986	*USEPA 660/3-75-009: Daphnia magna Acute Toxicity Test* Daphnia magna NOEC = <1.0 mg/L 24-hour LC50 = 6.5 mg/L **48-hr LC50 = 5.2 mg/L** (based on material dissolved in acetone)	Yes
Acute Toxicity to Algae	1987	*OECD 201: Alga. Growth Inhibition Test* Selenastrum capricornutum: NOEC = 0.10 mg/L **EbC50 = 0.36 mg/L** (based on material dissolved in acetone)	Yes
Mammalian Toxicity			
Acute Toxicity			
Oral	1981	**Rat: oral LD50 = 5000 mg/kg**	Yes
Dermal	1981	**Rabbit: dermal LD50 = >2,000 mg/kg**	Yes
Inhalation	1995	**Rat: inhalation 4 hr LC50 = 0.27 ppm**	Yes
Eye Irritation	1981	Mild Eye Irritant	Yes
Skin Irritation	1981	Moderate Skin Irritant	Yes
Dermal Sensitization	1981	Skin Sensitizer	Yes
Respiratory Sensitization	1984	No Sensitization Response Elicited	Yes
Repeat Dose Toxicity	1987	**(28 day inhalation) rat:** **NOEL = 0.38 mg/m^3**	Yes
	1990	(90 day inhalation) rat/mice: NOEL = Not Established	Yes
Developmental Toxicity		**No data**	**No Data**
Reproductive Toxicity	1981	Based on the results of the 90-day repeat dose inhalation study there were no macro or microscopic changes in any of the male or female reproductive organs that could be attributed to exposure to TMXDI. Thus suggestive that at the concentrations tested the material would not be a reproductive toxicant.	Yes
Genetic Toxicity: Gene Mutations	1983	Salmonella typhimurium: **Not mutagenic**	Yes
Genetic Toxicity: Chromosomal Aberration		**No data**	**No Data**

E. TEST PLAN FOR Isocyanic acid, m-Phenylenediiso-Propylidene, CAS# 2778-42-9

CAS# 2778-42-9	Data Available	Data Acceptable	Testing Required
Study	Y/N	Y/N	Y/N
Physical/Chemical Characteristics			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
Environmental Fate			
Photodegradation	Y	Y	N
Hydrolysis	-	-	N
Fugacity	Y	Y	N
Biodegradation	Y	Y	N
Ecotoxicity			
Acute Toxicity to Fish	Y	Y	N
Acute Toxicity to Invertebrates	Y	Y	N
Acute Toxicity to Algae	Y	Y	N
Mammalian Toxicity			
Acute Toxicity	Y	Y	N
Repeat Dose Toxicity	Y	Y	N
Developmental Toxicity	N	**No data**	**Y**
Reproductive Toxicity	N*	Y	N
Genetic Toxicity: Gene Mutations	Y	Y	N
Genetic Toxicity: Chromosomal Aberration	N	**No data**	**Y**

* - Results from the 90-day repeat dose inhalation study provide histopathology of male and female reproductive organs.

F. PHYSICAL CHEMICAL DESCRIPTION

1. MELTING POINT[1]

Test substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Determined from Specific Heat measurements, which were measured using a Perkin Elmer DSC 2 Differential Scanning Calorimeter and the technique of O"Neil with sapphire as the reference.
Results:	-10 °C (material is a clear colorless mobile liquid at room temperature)
Source:	Cytec Material Safety Data Sheet for TMXDI® (Meta) Aliphatic Isocyanate, MSDS# 2344, dated 12/01/1999.
Remarks:	The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997)[2].
References:	[1]Achorn, PJ, Haseltine, WG, and Miller JK (1986). Physicochemical properties of mono- and diisocyanates. J. Chem. Eng. Data, 31(4), 385-7. [2]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

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2. BOILING POINT

Test substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Determined by calculation from the analytically determined vapor pressure using isotenoscope technique[1].
Results:	292 °C (material is a clear colorless mobile liquid at room temperature)
Source:	Cytec Material Safety Data Sheet for TMXDI® (Meta) Aliphatic Isocyanate, MSDS# 2344, dated 12/01/1999.
Remarks:	The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al*. (1997)[2].

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Estimated by the MPBPWIN Program (v.1.40)[3], using the Adapted Stein and Brown Method.
GLP:	Not applicable to estimations
Year:	2002
Results:	320.10 °C
Remark:	The boiling point calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997)[2].
References:	[1]Achorn, PJ, Haseltine, WG, and Miller JK (1986). Physicochemical properties of mono- and diisocyanates. J. Chem. Eng. Data, 31(4), 385-7. [2]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59. [3]EPI Suite U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation, Syracuse, NY, 2000

3. VAPOR PRESSURE

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	ASTM D2879-83[1]
GLP:	no
Year:	1986
Results:	0.0032 mmHg @ 25 °C
Remark:	The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al*. (1997)[2].

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Estimated by the MPBPWIN Program (v.1.40)[3], using BP of 292°C and the Modified Grain Method.
GLP:	Not applicable to estimations
Year:	2002
Results:	0.00298 mmHg @ 25 °C (value consistent with measured value)
Remark:	The vapor pressure calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997)[2].
References:	[1]Achorn, PJ, Haseltine, WG, and Miller JK (1986). Physicochemical properties of mono- and diisocyanates. J. Chem. Eng. Data, 31(4), 385-7. [2]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59. [3]EPI Suite U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation, Syracuse, NY, 2000

4. PARTITION COEFFICIENT

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Estimated by the KowWin Program (v.1.66)[1]
GLP:	Not applicable to estimations
Year:	2002
Results:	Log Kow = 4.74
Remark:	The partition coefficient calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (1997)[2].
References:	[1]EPI Suite U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation, Syracuse, NY, 2000 [2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

5. WATER SOLUBILITY

Test substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Results:	Insoluble, reacts slowly with water to forming insoluble ureas.
Source:	Cytec Material Safety Data Sheet for TMXDI® (Meta) Aliphatic Isocyanate, MSDS# 2344, dated 12/01/1999.
Remarks:	The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al*. (1997)[1].

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Estimated from Kow with WSKOW (v1.40)[1] : KowWin Estimate
GLP:	Not applicable to estimations
Year:	2002
Results:	5.833 mg/L @ 25°C
Remark:	The water solubility calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (1997).[2]
References:	[1]EPI Suite U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation, Syracuse, NY, 2000 [2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

G. ENVIRONMENTAL FATE DATA

1. PHOTODEGRADATION

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Estimated by the AopWin program (v1.90)[1], which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere.
GLP:	Not applicable to estimations
Year:	2002
Results:	For reaction with hydroxyl radicals, the predicted half-life of the chemical is relatively rapid. Rate constant: 10.1332 x 10^{-12} cm^3/molecule-sec Half-life: 12.666 hours
Remark:	The photodegradation rate calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (1997).[2]

.

References:

[1]EPI Suite U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation, Syracuse, NY, 2000

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

2. HYDROLYSIS

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Estimated by the HYDROWIN program (v1.67)[1].
GLP:	Not applicable to estimations
Year:	2002
Results:	No estimate available.
	Remark: This program was not able to estimate a hydrolysis rate constant for this type of chemical structure. However, as manufactured, this material will react slowly with water resulting in the formation of insoluble ureas.
Reference:	[1]EPI Suite U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation, Syracuse, NY, 2000

3. TRANSPORT (FUGACITY)

Test Substance: Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9

Method: Estimated by the Level III Fugacity Model (Full-Output)

GLP: Not applicable to estimations

Year: 2002

Results: MacKay Level III Fugacity Model

Medium	Concentration %	Emissions (kg/hr)
Air	0.779	1000
Water	18.1	1000
Soil	62.6	1000
Sediment	18.5	0

Medium	Concentration %	Emissions (kg/hr)
Air	30.3	1000
Water	10.4	0
Soil	48.7	0
Sediment	10.6	0

Medium	Concentration %	Emissions (kg/hr)
Air	0.0401	0
Water	49.5	1000
Soil	0.0646	0
Sediment	50.4	0

Medium	Concentration %	Emissions (kg/hr)
Air	0.000324	0
Water	0.034	0
Soil	99.9	1000
Sediment	0.0346	0

Remark: The fugacity calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (1997).[2]

References: [1]EPI Suite U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation, Syracuse, NY, 2000

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

4. BIODEGRADATION

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	OECD Guideline 301D: Ready Biodegradability: Closed Bottle Test Due to the insolubility of the test article, sample aliquots were micro-pipetted onto a disc of glass fiber filter, which was then added directly to the test vessel. This ensured the immersion of the sample in the dilution water, increased surface area of exposure and avoided surface file and escape resulting from water partitioning. The solution was inoculated with a low concentration of microorganisms from a mixed population and kept in closed bottles in the dark at a constant temperature of 20 ± 1 degrees C. The activated sludge bacteria was from Bergen Co. New Jersey. The degradation was followed by oxygen analyses with the YSI Dissolved Oxygen Analyzer 54A over a 28-day period. Aparallel control with inoculum, but without test material, was run as a blank correction factor. The procedure was validated by means of a reference substance (aniline) of known biodegradability.
GLP:	yes
Year:	1988
Test Type:	Aerobic
Concentration Tested: Reference chemical:	Test chemical: 2 mg/ L Aniline: 2 mg/ L
Inoculum:	Activated Sludge Bacteria from Bergen County New Jersey, MUA (Fresh sewage treatment plant sample (per guideline))
Medium:	Sewage sludge (per guideline)
Results:	The test material was not found to be readily biodegradable by the OECD Closed Bottle Test. Degradation after 28-days was determined to be 13.7% as compared to 95% for the Aniline reference material. Because a level of 70% was not reached, this substance is not "Readily Biodegradable" by this test procedure.

Remark: The biodegradation rate calculated by an accepted method is assigned a reliability code of 1a according to the criteria established by Klimisch et al. (1997).[2] This was a GLP Guideline study.

References:

[1] United States Testing Company, Inc. Ready Biodegradability: The OECD Closed Bottle Test. Test Report 07154-1. May 4, 1988.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.

See Listing of Codes, p. 59.

H. ECOTOXICITY DATA

1a. ACUTE TOXICITY TO FISH[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	OECD Guideline 203: Fish Acute Toxicity Test
Type:	Static
Species:	Lepomis macrochirus (Bluegill sunfish, fresh water)
Exposure period:	96 hour(s)
Exposure Conditions:	-22.3°C, continuously monitored. -Diurnal light: ~15 hours light: ~ 9 hours dark with a gradual intensity conversion between periods. Daylight intensity ranged from 61.74 to 63.61 footcandles during full daylight periods.
Analytical monitoring:	Yes
Year:	1993
GLP:	The study was conducted following the intent of Good Laboratory Practices.
Results:	NOEC = >52.19 mg/L 96 hour LC50 = >65.88 mg/L (based on exposure to Water Accommodating Fraction, measured by analysis)
Remark:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997)[2]. Comparable to a guideline study.

Summary details:

The static fish bioassay was conducted in 8.5L glass vessels containing 3.2 liters Laboratory Dilution Water. Twenty (10 per 2 replicates) fish with a mean weight of 0.209 g and a mean length of 26 mm were used for each test concentration. A 48-hour range-finding test was conducted to determine the concentration range for the definitive study. The preliminary test concentrations were set at 0.005 g/L, 0.01g/L, 0.05 g/L, 0.1 g/L, and 1.0 g/L. Ten percent mortality was observed in the 0.1 g/L treatment after 48 hours. No mortality occurred in the remaining treatments during the 48-hour exposure period. Based on the results of the preliminary testing, five test concentrations were selected, 0.06, 0.12, 0.25, 0.5, and 1.0 g/L. Test concentrations were prepared by preparing a stock solution in deionized water and serially

diluting to obtain desired concentration. During mixing, clear globules of the test material were observed throughout the water column. An oily surface slick was also observed in all treatments. After the mixing period the water column appeared clear with clear globules of test material on the bottom. The water accommodating fraction (WAF) of each treatment solution was siphoned from the middle portion of the mixing container and divided into 2 replicate chambers. All results were based on the nominal concentrations.

The fish were observed once every 24 hours for mortality and abnormal effects. Water quality parameters of temperature, dissolved oxygen and pH were measured throughout the test and were within acceptable limits.

In general, the material persisted at eighty percent or greater when calculated measured values were compared. Total mortality was observed in one replicate of the 1.0 g/L treatment. Since no other mortality occurred during the 96-hour period, it is believed that the mortalities were caused by contamination of the test chamber.

References: [1]Exxon Biomedical Sciences, Inc. Laboratory Report # 142540 to Cytec Industries Inc., 1993.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

1b. ACUTE TOXICITY TO FISH[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 (~98-99% pure test material dissolved in acetone)
Method:	Based on methods outlined in the Committee on Methods for Toxicity Test with Aquatic Organisms, USEPA 660/3-75009. ABC Laboratories Protocol 7601.
Type:	Static
Species:	Pimephales promelas (Fathead minnow, fresh water)
Exposure period:	24-, 48-, and 96 hour(s)
Analytical monitoring:	Yes
Year:	1986
GLP:	Yes
Results:	NOEC = 0.32 mg/L

96 hour LC50 = 0.67 mg/L

Remark: This study is assigned a reliability code of 1a according to the criteria established by Klimisch *et al.* (1997)[2]. GLP guideline study.

Summary details:

The static fish bioassay was conducted in five-gallon glass vessels containing 15 liters of soft reconstituted water. 10 fish with a mean weight of 0.099 g and a mean length of 19 mm were used for each test concentration. The test vessels were kept in a water bath at 22 (±1) C. 24- and 48 -hour range-finding tests were conducted to determine the concentration range for the definitive study. The preliminary test concentrations were set at 1.0, 10.0, and 100 mg/L and at 0.01, 0.1 and 1.0 mg/L. Based on the results of the preliminary testing, five test concentrations were selected, 0.10, 0.18, 0.32, 0.56, and 1.0 mg/L. Also included was a dilution water control and a solvent control.

Test concentrations were prepared by preparing a stock solution in deionized water and serially diluting to obtain desired concentration. The 0.32, 0.56 and 1.0 mg/L solutions had a very light surface film after stirring but the film was no longer visible after 24 hours of testing. All results were based on the nominal concentrations.

The fish were observed once every 24 hours for mortality and abnormal effects. Water quality parameters of temperature, dissolved oxygen and pH were measured throughout the test and were within acceptable limits. The 24-, 48-, and 96- hour LC50 values for TMXDI were 0.70, 0.67, and 0.67 mg/L, respectively. The no-effect concentration for the test material, based on the lack of mortality and abnormal effects, was estimated to be 0.32 mg/L after 96 hours. The abnormal effects of mortality, surfacing, loss of equilibrium and/or quiescence were observed in the 0.56 and 1.0 mg/L concentrations during the 96-hr period. Statistical analysis of the concentration vs. effect data was obtained by employing a computerized LC50 program developed by Stephan, 1978[3]. This program calculated the LC50 statistic and its 95% C.L. using the binomial and the moving average tests, respectively. The method of calculation selected for use was that which gave the narrowest confidence limits for the LC50.

References:

[1]ABC Laboratories Report # 34329 to American Cyanamid Company, 1986.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

[3]Stephan, C.E., Busch, K., Smith, R., Burke, J. and Andrew, R. A computer program for calculating an LC50. U.S. E.P.A., Duluth, Minnesota, pre-publlication manuscript, August, 1978.

2. ACUTE TOXICITY TO AQUATIC INVERTEBRATES[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 (~98-99% pure test material dissolved in acetone)
Method:	Based on methods outlined in the Committee on Methods for Toxicity Test with Aquatic Organisms, USEPA 660/3-75009. ABC Laboratories Protocol 7806.
Type:	static
Species:	Daphnia magna (Crustacea)
Exposure period:	24 and 48 hour(s)
Analytical monitoring:	Exposures based on nominal concentrations
Year:	1986
GLP:	Yes
Results:	NOEC = <1.0 mg/L 24-hour LC50 = 6.5 mg/L 48-hr LC50 = 5.2 mg/L
Remark:	This study is assigned a reliability code of 1a according to the criteria established by Klimisch et al. (1997)[2]. GLP guideline study.

Summary details:

The static Daphnia magna bioassay was conducted in 250 ml glass beakers, 10 daphnids/ beaker, containing 200 ml of ABC well water. These vessels were kept at 20 (± 2) °C. The lighting was maintained at 50-70 foot-candles on a 16 hour daylight photoperiod. An initial range-finding test was conducted to determine the concentration range for the definitive study. The preliminary test concentrations were set at 1.0, 10 and 100 mg/L. Based on the results of the preliminary testing, five test concentrations were selected and tested in duplicate, 0 (control), solvent control, 1.0, 1.8, 3.2, 5.6, and 10 mg/L. Test concentrations were prepared by preparing a stock solution in deionized water and serially diluting to obtain desired concentrations. All results were based on the nominal concentrations. Water quality parameters of temperature, dissolved oxygen and pH were measured at the termination of the test and were within acceptable limits. The dissolved oxygen concentrations, which ranged between 8.2 and 8.9 mg/l, were considered adequate for testing. The pH values of the treated chambers were consistent with the control and ranged form 8.2 to 8.3. The no-effect concentration based on the lack of mortality and abnormal effects was <1.0 mg/l after 48 hours, since the abnormal effects of mortality, quiescence, surfacing and/or daphnids lying on the bottom were observed in all test concentrations. The single mortality in the

control was considered aberrant. The 24- and 48-hour LC50 values for TMXDI were 6.5 and 5.2 mg/L. Statistical analysis of the concentration vs. effect data was obtained by employing a computerized LC50 program developed by Stephan, 1978[3]. This program calculated the LC50 statistic and its 95% C.L. using the binomial and the moving average tests. The method of calculation selected for use was that which gave the narrowest confidence limits for the LC50.

References:

[1]ABC Laboratories Report # 34330 to American Cyanamid Company, 1986.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

[3]Stephan, C.E., Busch, K., Smith, R., Burke, J. and Andrew, R. A computer program for calculating an LC50. U.S. E.P.A., Duluth, Minnesota, pre-publlication manuscript, August, 1978.

3. TOXICITY TO AQUATIC PLANTS[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	OECD Guideline 201: Alga, Growth Inhibition Test.
Special Preparation:	Sample was diluted in anhydrous acetone v/v and stored in dark until use; Controls contained 10 microliters of acetone; Maximum dissolved solvent added was 10 microliters/flask.
Species:	Selenastrum capricornutum (Algae), Strain #22662
Endpoint:	Growth rate
Exposure period:	96 hour(s)
Incubation:	21-22 degrees C, continuous light, approximately 8000 Lux, shaking culture.
Analytical monitoring:	Exposures based on nominal concentrations
Year:	1987
GLP:	Yes
Results:	NOEC = 0.10 mg/L EbC50 = 0.36 mg/L (C.L. = 0.24- 0.52 mg/L)
Remark:	This study is assigned a reliability code of 1a according to the criteria established by Klimisch et al. (1997)[2]. GLP guideline study.

Summary details:

Temperature and light readings were measured throughout the test and were within acceptable limits. The static algal toxicity study on *Selenastrum capricornutum* was conducted in 250 mL Erlenmeyer flasks containing 100 mL of Sterile OECD Algal nutrient medium. This media was composed of 10.0 mL of a salt solution diluted to a final volume of 1,000 mL of deionized water. To each flask was added a starting algal inoculum containing 1×10^4 cells/ml. The test vessels were incubated for 96 hours at 21-22 ± 2°C under continuous "cool white" fluorescent light and constant shaking. Temperature and light intensity were monitored throughout the study. Based on the results of the range-finder, test concentrations were set at 0, 0.32, 1.0, 3.2, 10.0, and 32 mg/L. Test flasks were prepared in triplicate for each test concentrations and the control. Test concentrations were prepared by preparing a stock solution in deionized water and serially diluting to obtain desired concentration.

Linear regression analysis, plotting percent growth versus log of concentration, yielded a 96 hr EC50 of 2.1 ppm and a NOEC of 0.34 ppm. Cell growth was insufficient at 24 and 48 hours to establish concentration-effect relationships for all concentrations and for the blank control. The median effects, therefore, could not be calculated for these time periods.

The calculated correlation coefficients indicate that the 96hr value may be the better estimate of the median algal inhibitory concentration due to more developed cell growth with time and thus better enumeration and differentiation among test concentrations.

The rate of cell growth was satisfactory (greater than 16 x inoculum level at 72 hrs) in controls for acceptable data transformation. The se of the solvent produced a slight "lag" in the growth of cells but did not depress the population to a degree sever enough to confound the concentration effects.

References: [1]United States Testing Company, Inc. Laboratories Report # 6498-1 to American Cyanamid Company, 1987.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

I. MAMMALIAN TOXICITY

1. ACUTE TOXICITY

A. ACUTE ORAL TOXICITY[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 (91.58% Purity)
Method:	Oral Gavage LD50 Toxicity Study in Rats
Type:	oral LD50
Species/Strain:	rat/ Sprague-Dawley
Sex:	male/female
Number of animals:	60
Vehicle:	none
Year:	1981
GLP:	no
Results:	LD50 = 5000 mg/kg (males); 4,600 mg/kg (females)
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997). Meets generally accepted scientific standards and is described in sufficient detail.

Summary details:

Animals housed individually at room temperature, fasted overnight before dosing. Test material was administered undiluted. Animals dosed by oral were observed frequently post-dosing and twice daily thereafter for physical condition and mortality. Physical examinations were performed pre-dose. Body weights were recorded on days –1, 1, 2, 3, 4, 7, 11, and 15 or at time of death if prior to scheduled termination of study. All animals found dead or surviving to day 15 were subjected to a complete gross necropsy.

Sixty rats (5/per sex/per dose) received neat TMXDI by gavage at a concentrations of 0, 2.8, 3.6, 4.5, 5.6, and 7.1 ml/kg. Mean body weight data were compared between untreated and treated animals, treated animals gained less weight than controls and lost weight for 1 to 3 days post-dosing. Clinical signs did not appear to increase in frequency or variety with increased dose level, did not exhibit any sex related trends, and included diarrhea, crusty material around anus, soft stool, crusty material around face, paws, eyes, nose, and scrotum, cream-colored material around mouth, alopecia, swollen feet, edema around anus, nasal discharge, red-colored nasal

discharge, tachypnea, lacrimation, lethargy, urine-soaked fur, piloerection, ataxia, moribund, cold body temperature, and tremors. Untreated controls appeared normal throughout study.

Necropsy findings did not exhibit any apparent dose related or sex related trends.

References: [1]Acute Oral Toxicity of TMXDI, Report #81-159. Biosphere Research Center for American Cyanamid Company, December 31, 1981.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

B. PILOT ACUTE ORAL TOXICITY[1]

Test Substance: Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9

Method: Pilot Oral Gavage LD50 Toxicity Study in Rats

Type: oral LD50

Species/Strain: rat/ Sprague-Dawley

Sex: male/female

Number of animals: 10

Vehicle: none

Year: 1981

GLP: No

Results: LD50 = > 5000 mg/kg bw

Remark: This study is assigned a reliability code of 2e according to the criteria established by Klimisch et al. (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

Summary details:

Animals housed individually at room temperature, fasted overnight before dosing. Test material was administered undiluted. Animals dosed by oral gavage and observed at 20 minutes, 1 hour, 2 hours, and 4 hours post-dosing and twice daily through day 13 for physical condition and

mortality. Physical examinations were performed pre-dose. Body weights were recorded on days –1, 0, 1, 2, 3, 6, 10, and 14. All animals surviving to day 1 5 were subjected to a complete gross necropsy by examining the organs of the thoracic, abdominal, and cranial cavities.

Ten rats (5/sex) received neat TMXDI by gavage at a concentration of 5000 mg/kg. No signs of toxicity were observed on the day of dosing. Soft feces, inactivity, wet peri-anal area, crusty muzzle were noted in most of the animals from day 1 through day 3. The wet per-anal area persisted to termination of the 15-day study. Two females were found dead on day 2 of this study. Sings of toxicity observed prior to death were sedation, soft feces and wet peri-anal area. Postmortem examination revealed irritation of the intestinal mucosa. With the exception of these two females, all other animals showed an overall weight gain. Gross postmortem examination of the 8 survivors at terminal sacrifice revealed irritation of the small intestinal mucosa in 3 animals. There were no other significant findings attributable to TMXDI.

References:

[1]Acute Oral Toxicity of TMXDI, Report #18750. American Cyanamid Company, June 29, 1981.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

C. ACUTE DERMAL TOXICITY[1]

Test Substance: (Batch: S-13708-76)	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Acute Dermal LD50 Study according to the Method of Draize et al., 1944.
Type:	dermal LD50
Species/Strain:	rabbit/ New Zealand Whites
Sex:	male/female
Number of animals:	10
Vehicle:	none
Year:	1981
GLP:	no
Results:	LD50 = 2000 mg/kg
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997)[3]. Meets generally accepted scientific standards and is described in sufficient detail.

Summary details:

A single dose of 2000 mg/kg was administered topically to the abraded skin of 10 rabbits (5/sex) and was maintained in contact with the skin for 24 hours with an occlusive wrap. All animals were observed twice daily throughout the study. Body weights were obtained on days –1, 0, 1, 2, 3, 10 and 14. Physical examinations were performed on day –1. On day 14 all surviving animals were humanely killed and gross postmortem examinations were performed. Samples of the treated skin were retained.

One death occurred on day 4 but no specific signs of systemic toxicity were observed.

The degree of dermal irritation was scored on days 1, 2, 3, 4, 7 and 14 with the Draize technique. Dermal irritation was observed and was maximal 14 days after dosing, with a mean score of 3.9 out of 4. Significant irritation and eschar formation was evident at day 4 and persisted until terminal sacrifice.

Gross port-mortem examination revealed no significant findings related to treatment except for scabbing and eschar formation. There were no remarkable changes in body weights.

References:

[1]Acute Dermal Toxicity of TMXDI, Report #18750. American Cyanamid Company, June 29, 1981.

[2]Draize, J.H., Woodward, G. and Calvery, H.O.: Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Therap. 82: 377-390, 1944.

[3]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

D. ACUTE INHALATION TOXICITY

i. 1-HOUR EXPOSURE[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Acute Toxicity of Inhaled TMXDI in the Guinea Pig (Whole-body exposure)
Type:	Inhalation LC50
Species/Strain:	Guinea Pig/English Smooth- Haired (Cavia porcellus)
Sex:	male/female
Number of animals:	50
Exposure time:	1 hour
Year:	1982
GLP:	yes
Results:	1 hour inhalation LC50 = 0.240 (0.190 to 0.303) ppm
Remark:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997)[2]. Comparable to a guideline study.

Summary details:

Each group, containing five male and five female guinea pigs, was exposed once for 1 hour to an aerosol generated from the test article. The animals were placed in the chamber and the aerosol generator was allowed to equilibrate for 10-minutes followed by a 50-minute period of continuous operation. The generator was then turned off and the animals were removed from the chamber after another 10 minutes. The exposure levels were obtained by adjusting the rate at which the test article was supplied to the generator. Nominal chamber calculations were calculated from the weight loss from the generator and the total airflow through the chamber during the 1-hour exposure period. Chamber concentrations and particle size distribution were measured analytically. Gravimetric chamber concentrations and Gas Chromatograph Analysis were used to analytically determine the test chamber concentrations. Particle size was assessed using a May Cascade Impactor and an optical counting and sizing procedure of Casella & Co. Ltd. Temperature and relative humidity in the inhalation chambers were monitored. Airflow was set at 45L/min. A slight negative pressure within the chamber with respect to room atmosphere was maintained.

Clinical signs were observed for all groups on the day of exposure and twice daily during the 14-day recovery period. Body weights were determined on the day prior to treatment and on days 2, 3, 4, 7 and 14 of the study. All surviving animals were subject to a detailed gross pathology examination.

Chamber concentrations tested were 0, 0.195, 0.233, 0.355, and 0.457 mg/L. The count median diameter of the particles ranged from 1.7 to 3.0 micrometers. 0/5, 1/5, 3/5, 5/5, and 5/5 males died and 0/5, 2/5, 2/5, 3/5, and 5/5 females died during the study period. Clinical signs observed in surviving animals during the first three days post-exposure consisted of weakness, lethargy, gasping/rales, and discharge from eyes, nose or mouth. Body weight losses occurred in all treatment groups. Gross pathology revealed swollen, reddened, rubbery lungs and lung congestion in animals that died. Swelling, reddening, increased consistency, collapse and foci of discoloration were observed at termination in survivors.

The LC50 value and the 95% CI were calculated using the method of Litchfield and Wilcoxon, Journal of Pharmacology & Experimental Therapeutics, 1949, 96(2), 99-113. The calculations were based on concentrations of test article measured analytically.

References:

[1]Bio-Research Laboratoreis Ltd., Report # 81182 for Cyanamid Canada Inc., 1982.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

ii. 4-HOUR EXPOSURE[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 (99.3% pure material; Lot #348)
Method:	OECD Guideline 403 "Acute Inhalation Toxicity"
Type:	LC50
Species/Strain:	rat/ Sprague-Dawley
Sex:	male/female
Number of animals:	50
Exposure time:	4 hour(s)
Year:	1995
GLP:	yes
Results:	4-hour inhalation LC50 = 0.027 mg/L or 0.27 ppm
Remark:	This study is assigned a reliability code of 1a according to the criteria established by Klimisch et al. (1997)[2]. It was a GLP study conducted under OECD guidelines.

Summary details:

Each group, containing 5 male and 5 female rats, was exposed continuously for 4 hours to an atmosphere containing droplet aerosol and vapor of TMXDI. The animals were placed in whole-body exposure chambers within a large cabinet. The test atmosphere entered through a port at the base of the chamber and passed out through small holes in the lower edge of the square section. A supply of clean, dried air, was connected to the generator and the supply pressure was adjusted to a flow rate of 15 L/min. The total chamber air flow was made up to 25 L/min. Airflow was monitored throughout the exposure using in-line flow meters. The aerosol generator was allowed to equilibrate for 11-minutes followed by a 4-hour period of continuous operation. The generator was then turned off and the animals were removed from the chamber after the chamber was allowed to clear. The exposure levels were obtained by adjusting the rate at which the test article was supplied to the generator. Seven air samples were taken during each exposure and analyzed for TMXDI concentration. Chamber concentrations and particle size distribution was measured analytically. Temperature and relative humidity in the inhalation chambers were monitored. The mean concentrations of droplet aerosol and vapor concentrations tested were Group 1: Control, Group 2: 0.316 mg/L, Group 3: 0.0935 mg/L, Group 5: 0.0533 mg/L, and Group 6: 0.02 mg/L. Group 4 received a large overdose during the last hour due to technical failure. These rats were removed from the study immediately following the exposure period and humanely killed. The particle size distribution as MMAD (micrometers) for the exposure concentrations were 2.7, 2.7, 3.2, and 3.5, resulting in 91, 91, 87, and 80% respirable fractions, respectively.

The rats were observed continuously for clinical signs of reaction to the test substance during exposure and at least twice daily throughout the observation period. The clinical signs wre recorded at the end of the chamber equilibration period, at 0.25, 0.5 and 1 hour and then at hourly intervals during exposure. During the observation period, the clinical signs were recorded once in the morning and then as necessary following a later check for clinical signs. Body weights were determined daily from the date of receipt of the animals until the end of the observation period. All surviving animals were subject to a detailed macroscopic examination. The lungs were removed, dissected clear of surrounding tissue and weighed to calculate lug weight to body weight ratios. The lungs and all macroscopic abnormalities were preserved.

The mortality data is summarized as follows:

Group	Males	Females	Total
Group 1: Control	0/5	0/5	0/10
Group 2: 0.316 mg/L	5/5	5/5	10/10
Group 3: 0.0935 mg/L	5/5	5/5	10/10
Group 5: 0.0533 mg/L	5/5	4/5	9/10
Group 6: 0.02 mg/L	2/5	1/5	3/10

Clinical signs observed in during exposure to TMXDI included respiratory abnormalities (exaggerated respiratory movements and/or irregular respiration), a partial closing of the eyes and a reddening of the ears and feet. Additional signs seen in rats exposed at 0.316 mg/L included piloerection, wet fur and restless behavior. During the observation period clinical signs included death, respiratory abnormalities (exaggerated respiratory movements, noisy respiration and/or gasping) a partial closing of the eyes and peripheral vasodilation. In addition, whole-body hypothermia, a red/brown discharge from the snout, immobility, emaciation, a swollen abdomen, lethargy, a dark appearance of the eyes, salivation, red/brown staining around the snout and jaws, wet fur around the snout, jaws and the head, and matted appearance of the fur were seen in some groups exposed to TMXDI.

The majority of decedent rats exposed lost weight prior to death. The female rat surviving exposure at 0.0533 mg/L failed to gain weight normally during the observation period. The rat of bodyweight gain for rats surviving exposure at 0.02 mg/L was reduced for two days, subsequently gain for this group was similar to that of the control rats.

The lung weight to bodyweight ratios for the majority of surviving and decedent rats were higher than the control values. The ratios for the surviving test rats at 0.02 mg/L were within normal limits. Abnormalities seen in decedent rats exposed included minimal to marked congestion of the lungs, a swollen appearance of the lungs, a white frothy fluid in the trachea, a fluid-filled thoracic cavity, distension of the gastrointestinal tract with gas, opacities of the eyes and red/brown staining around the snout and jaws. Minimal to moderate congestion of the lungs was the major finding in rats surviving exposure.

References: [1]Acute Inhalation Toxicity in Rats, 4-hour Exposure. Huntingdon Research Centre Report # CTI 5/950879 for Cytec Industries Inc, 1995.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

E. PRIMARY EYE IRRITATION STUDY[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 Batch S-13708-76
Method:	Primary Eye Irritation Study according to the Method of Draize et al., 1944.
Type:	Primary Eye Irritation
Species/Strain:	Rabbits
Sex:	female
Number of animals:	9
Year:	1981
GLP:	Conducted Under Spirit of GLP with Quality Assurance Compliance Audit Documented.
Results:	Mild eye irritant
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997)[3]. Meets generally accepted scientific standards and is described in sufficient detail.

Summary details:

A single dose of 100 microliters of undiluted TMXDI was placed in the cupped lower lid of the right eye of each rabbit; the left eye served as an untreated control. Once group of six rabbits received no further treatment. A second group of three rabbits had the right eyes rinsed with water for 60 seconds, 30 seconds after instillation of the compound. During the 15 day study, the eyes were examined for discharge, chemosis, inflammation, and opacity on days 1,2,3,4,7,10 and 13 after dosing and Ocular Irritation Scores (Draize Scores) were calculated. All rabbits survived and gained weight. The animals were humanely killed without necropsy on day 14.

Ocular exposure produced no corneal damage at any time in the rabbit's eyes. All treated eyes responded to light and in iridal score was observed in any rabbits. However, discharge, chemosis and redness of the conjunctivae were observed in all animals with either washed or unwashed eyes. Rinsing the eye with water lessened irritation. Irritation to the conjunctivae appeared to dissipate but still persisted at the termination of the study. The average of the Draize Irritation Scores for 24, 48 and 72 hours was 15.1 and 13.6 on a scale of 110 for the six washed and three unwashed eyes, respectively.

References: [1]American Cyanamid Company, Wilbur Malcolm Toxicology Laboratories, Report # 81131, 1981.

[2]Draize, J.H., Woodward, G. and Calvery, H.O.: Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Therap. 82: 377-390, 1944.

[3]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

F. PRIMARY DERMAL IRRITATION STUDY[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9
Method:	Primary Dermal Irritation Study according to the method described in Federal Register Volume 43, 37336, Part 163.81-5 and Federal Register Volume 44, 44054, Part 772.112-25.
Type:	Primary Dermal Irritation
Species/Strain:	Rabbits
Sex:	male
Number of animals:	6
Year:	1981
GLP:	Yes.
Results:	Primary Irritation Index = 3.3 Moderate Skin Irritant
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997)[2]. Meets generally accepted scientific standards and is described in sufficient detail.

Summary details:

The test sites were prepared by closely clipping the hair of two sites on the right side of the rabbit's spine and two on the left side. 24 hours after clipping the hair, 2 of the application sites were mechanically abraded. A single 0.5 ml dose of the test article was applied to a 1-inch square gauze patch and applied to each of the 4 test sites (2 abraded and 2 intact) on each animal. The patches were held in place with tape and covered with a n occlusive binder. The binder was removed 24 hours later, the test sites were wiped (not washed) to remove remaining test article. Skin reactions were evaluated ~2 hours after wiping.

The animals were observed twice daily and skin reactions were scored at ~24 and 72hours and daily thereafter until 13 days post-dose. With the exception of moderate sin irritation, all animals appeared normal throughout the study. At the 24- and 72-hour evaluations, scores for erythema ranged from very slight to sever for intact sites and form well-defined to sever for abraded sites. Scores for edema ranged from none to slight for both intact and abraded sites. There were no important differences in skin irritation between intact and abraded sites.

Since all animals exhibited skin irritation at 72 hours, gradings continued until day 13. By day 6, all sites in all animals showed eschar formation, which persisted, at all but two sites on one animal. The study was terminated at day 13.

References:

[1]Biosphere Research Center, Report #81-158 for American Cyanamid Company, 1981.

[2]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

G. DERMAL SENSITIZATION STUDY[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 Batch S-13926-25-3A
Positive Control:	Isophorene diisocyanate (IPDI)
Vehicle:	Olive Oil
Method:	Dermal Sensitization Study
Species/Strain:	Hartley Albino Guinea Pigs
Sex:	male
Number of animals:	30
Year:	1981
GLP:	Yes.
Results:	Contact sensitization was evident at initial challenge (5 days post-induction). Evidence of sensitization was negligible upon rechallenge (14 days post-induction).
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997)[2]. Meets generally accepted scientific standards and is described in sufficient detail.

Summary details:

Primary Irritation (Range-finding): Prior to initiation of the induction phase, the primary irritation potential was determined. Five animals were each exposed to 5 dilutions (0.10, 0.05, 0.025, 0.0125, 0.00625 and 0.00%) of either test article or positive control substance. Twenty-five microliters of each dilution and the undiluted vehicle were epicutaneously applied to each animal by gentle inunction. No patch was applied. All animals appeared normal except for skin irritation. Two of 5 animals treated with IPDI exhibited skin reactions. By 48 hrs the reactions were all grade 1 erythemas. All other test sites appeared normal. Three of 5 animals treated with TMXDI exhibited erythema reactions. No skin irritation was observed at TMXDI concentrations of 0.0125% or below.

Induction: Based on the result of the irritation phase, the induction phase was initiated. Single applications of 0.36 molar concentrations of TMXDI and IPDI in olive oil were applied to 10 animals each (two sites per animal) in 25 microliter aliquots by gently inunction. No patch was applied.

Challenge: Five days after the single induction application, each animal was exposed to the same concentration of either TMXDI or IPDI. Twenty-five microliters of each dilution and the

undiluted vehicle were epicutaneously applied to each animal at previously untreated sites. No patch was applied. At challenge, test sites were not rotated.

Rechallenge: Nine days after the initial challenge, the animals were subjected to a rechallenge. Test sites used at rechallenge had not been previously used. IPDI was applied to all animals. TMXDI was applied only to those animals, which had been previously challenged with this test article.

Observations: All animals were observed twice daily for clinical signs. Skin condition was evaluated at ~24 and 48 hrs after each application. Initial body weights were obtained prior to primary skin irritation determinations and the induction phase. Terminal body weights were obtained after skin sites were evaluated for animals used to determine the primary skin irritation and 2 days after the last 48-hr evaluation (rechallenge phase).

Gross Necropsy was performed on the animal found dead.

Evidence of a sensitization response was considered to be skin reactions at sites treated with non-irritating concentrations of the test articles or enhanced skin reactions at sites treated with irritating concentrations.

Results: Four of 10 animals used for the primary skin irritation phase showed some degree of weight loss over the three-day test period. All animals that survived the main study gained weight. During the main study (between challenge and rechallenge), one male challenged with IPDI was found dead. The cause of death could not be determined.

Contact sensitization was evident for both articles at initial challenge (5 days post-induction). Evidence of sensitization for both articles was negligible upon rechallenge (14 days post-induction).

References:

[1]Biosphere Research Center, Report #81-149 for American Cyanamid Company, 1981.

[2]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

H. RESPIRATORY SENSITIZATION STUDY[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 Batch S-14536-86-1, Lot#7
Control:	Guinea Pig Serum Albumin (GPSA) Lot#53F-93991
Vehicle:	Dry acetone for inhalation component/ saline for intradermal component
Method:	Dermal Sensitization Study
Species/Strain:	English smooth-haired guinea pigs
Sex:	female
Number of animals:	24
Year:	1984
GLP:	Yes
Results:	Intradermal and respiratory challenges did not elicit any response indicative of sensitization.
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997)[2]. Meets generally accepted scientific standards and is described in sufficient detail.

Summary details:

Twelve animals were randomly allocated to each the test and control group and housed individually. Animals were selected from a starting group of 48 based on their intermediate respiratory rates (in the range of 98 to 129 breaths/min). The group size exceeded the number that could be accommodated simultaneously therefore the groups were divided in 3 subgroups each of 4 animals.

Induction: Animals were placed in whole body exposure chambers. Airflow through the 150-L chamber was set at 45 L/min and was measured in the exhaust line by means of a ball-type flowmeter. A slight negative pressure within the chamber with respect to the room atmosphere was maintained. Each guinea pig was exposed for 3 hours on study days 1 – 5 to an aerosol of TMXDI at a target concentration of 36 micrograms/L (concentration selected based on results of range-finding study). Aerosols were generated using Pitt No. 1 generators each fitted with an elutriator. The generators were supplied with 4% v/v TMXDI dissolved in dry acetone, from a syringe pump, and dry compressed air. Make-up air not provided by the compressed air line was conditioned room air. Compressed air to operate the atomizer was supplied by a Sihi air compressor and the air was dried in Hankinson's refrigerated air dryers prior to passage through

the aerosol generator. Temperature and relative humidity in the exposure chambers were monitored at intervals during the induction exposure by means of sensors located inside the chamber.

Challenge: On study days 22, 23 and 26, animals were exposed nose-only to an aerosol of TMXDI/GPSA at a target concentration of 0.015-0.020 mg/L for a 20-minute period. The control animals were similarly exposed to the same aerosol. Airflow through the 10-L nose-only chamber was set at 17L/min and was measured in the exhaust line by means of a ball-type flowmeter. A slight negative pressure within the chamber with respect to the room atmosphere was maintained.

Aerosols were generated using Pitt No. 1 glass nebulizer without an elutriator. Compressed air to operate the atomizer was supplied by a Sihi air compressor and the air was pre-dried in Hankinson's refrigerated air dryers prior to passage through the aerosol generator.

Chamber Concentrations were determined analytically from air sample drawn on study days 1 to 5. Nominal concentrations for study days 1 to 5 were calculated from total weight of test article consumed during each exposure and total airflow through the exposure system. On study days 22, 23, and 26 air sample concentrations were determined gravimetriclly and by calculation. Overall mean for the analytically determined concentrations was 26.7 micrograms/L (target was 36 micrograms/L). Challenge exposure chamber concentrations were a little above, but within acceptable limits of the target range.

Particle Size distribution was measured on day 5 of exposure and a separate analysis was performed for the corresponding GPSA complex. Particle size MMD was determined to be 1.6 (2.4GSD) and 0.8 (2.5GSD), respectively.

Clinical Signs: All animals were observed during and immediately after exposure and during recovery period on each day of exposure. Each animal was observed daily throughout the study period. Body weights were determined on the day of randomization, on the first day of exposure prior to treatment, and on days 8, 15 and 22 of the study and on the day of necropsy.

Lethargy and nasal and oral discharge was observed in both treated groups during the induction exposures. Nasal or oral discharge persisted on the days following exposures in 1 animal. There were no other treatment related clinical abnormalities. There were no statistically significant differences in body weight between the treatment animals and controls.

Respiratory Rates: None of the animals showed an increase in respiratory rate equal to or greater than the value 36% used as a threshold as evidence of a positive response. The was, therefore, no evidence of sensitization.

Hisotpathology: There were no treatment-related effects revealed in the lung weight data.

Skin Sensitization: On study day 24 the animals were challenged for skin sensitization potential. TMXDI-GPSA was dissolved in saline to give a 0.0333% concentration. GPSA alone in sterile saline was used as the control. Preliminary work indicated that 0.3% TMXDI-GPSA was the highest non-irritating concentration. The animals were intradermally dosed with 100 microliters of test material and control substance at different sites. Intradermal route was selected in order

to assess immediate hypersensitivity. There was no evidence of sensitization as evidenced by the absence of scores equal to or greater than 2 for erythema.

References:

[1]Bio-Research Laboratories Ltd., Report #81-187/88 for American Cyanamid Company, 1984.

[2]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

2. REPEATED DOSE TOXICITY[1]

A. SUBACUTE INHALATION TOXICITY

4-WEEK EXPOSURE[1]

Test Substance:	Respirable aerosol of TMXDI, CAS# 2778-42-9 (98% Isocyanic acid, m-phenylenediiso-propylidene in acetone) LOT UC-0053
Method:	Whole Body Chamber Exposure: 4-Week Inhalation Toxicity Study.
Type:	4-Week Inhalation Toxicity Study
Species/Strain:	rat/Sprague-Dawley
Sex:	male/female
Number of animals:	40
Exposure time:	6 hours per day, 5 days per week, for 4 weeks
Year:	1988
GLP:	yes
Results:	All animals survived the duration of the study at all concentrations tested.
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997)[2]. Meets generally accepted scientific standards and is described in sufficient detail

Summary details:

This study was designed to assess the toxic effects of TMXDI when administered by inhalation as a respirable aerosol to groups of rats. Each group, (5/sex/group), was exposed for 6 hours per day, five days per week, for four weeks at target concentrations of 0.5, 1.5 and 5.0 mg/m3. Control animals (5/sex) received a vapor exposure to acetone only. Animals received a total of 22 exposures (2 additional exposures were added due to low exposure concentrations obtained on Days 1 & 2 of exposure). Aerosol exposure levels were monitored by impingers analyzed by HPLC four times per chamber per day; in addition, vapor levels were monitored by MIRAN® four times per chamber per day. Particle size distribution measurements were made twice each day using a TSI Aerodynamic Particle Sizer. Physical observations for abnormal signs were made during exposure for all animals. Detailed physical examinations were recorded pretest and before the first and last exposure each week on Test Days 1, 5, 8, 12, 15, 19, 22 and 26; body weight measurements were also obtained just prior to sacrifice on Test Day 29. Just prior to

sacrifice, blood samples were obtained for hematology and clinical chemistry, then all animals were sacrificed, selected organs were weighed and organ-to-body weight ratios were calculated. Complete gross postmortem examinations were conducted on all animals. Microscopic examination of selected tissues was performed on all animals (tissues included the male and female reproductive organs).

During non-exposure animals received food and water ad libitum. Room temperature (22±3°C) was monitored and recorded twice daily. Relative humidity was maintained between 30-70%, monitored and recorded twice daily. The animal rooms were kept to a 12 hour light/dark cycle.

Exposure was via the inhalation route, administered in the breathing zone as a respirable aerosol with a vapor solvent.

The cumulative mean analytical exposure concentrations as determined by liquid impingers were 0.00, 0.38. 1.5, and 4.4 mg/m^3 of TMXDI in acetone, with an average nominal concentrations of 230, 230, 220 and 200 mg/m^3 of TMXDI in acetone for the control, low-, mid-, and high-dose groups, respectively. The cumulative mean analytical exposure concentrations of acetone vapor as determined by MIRAN® analysis were 190, 190, 190 and 180 mg/m^3 for the vehicle control, low-, mid-, and high-dose groups, respectively. Particle size distribution determinations indicated the test aerosol atmosphere was respirable.

All animals survived the duration of the study.

Physical observations indicated evidence during exposure of reduced activity of increasing incidence with increase of exposure for all levels, and occasional evidence of secretory responses during non-exposure periods which were possibly dose-related.

Body weight measurements showed a statistically significant decrease in males exposed to the high level, prior to sacrifice after the last exposure. While no prior body weight measurements showed statistically significant changes, lower body weights were evident for both sexes exposed to the high-dose beginning around Test Day 5-8.

There were no significant changes or trends relative to hematologic evaluations. Clinical chemistry test showed no effects except for a slight, but statistically significant increase in serum calcium and phophorous levels of males exposed to the high concentration; female rats showed a similar trend for these parameters but changes were not statistically significant.

Terminal organ weight and organ-to-body weight ratios showed a statistically significant elevation of relative lung weights for females exposed to the high concentration; absolute lung weights showed a dose-related trend toward elevation but they were not statistically significant. There were no other differences felt to be due to exposure.

Gross portmortem evaluations showed evidence of discolored lungs in one of five males exposed to the low-level, one male and 1 female (out of five each) exposed to the mid-level and four of five males exposed to the high-level. Microscopically, the significant findings were subacute/chronic inflammations of the lungs only in some high-level animals, and the

appearance of hyperplastic and metaplastic changes in the bronchi of several high-dose animals which is suggestive of a dose–related effect. These changes were not seen in animals from the control or the two lower exposure levels.

References:

[1]Bushy Run Research Center Report # 51-611 for American Cyanamid Company, 1988.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

B. SUBCHRONIC INHALATION TOXICITY

14-WEEK EXPOSURE[1]

Test Substance:	Respirable aerosol of TMXDI, CAS# 2778-42-9 (98% Isocyanic acid, m-phenylenediiso-propylidene in acetone) BRRC # 50-483 A to H
Method:	14-Week Vapor Inhalation Study with Rats and Mice.
Type:	14-Week Whole-body Inhalation Toxicity Study
Species/Strain:	rat/Sprague-Dawley Mice/CD-1
Sex:	male/female
Number of animals:	80 rats/80 mice
Exposure time:	6 hours per day, 5 days per week, for 13 weeks
Exposure concentrations:	0, 0.4, 0.8, or 1.6 ppm (mean analytical concentrations were 0.31, 0.72, and 1.46 ppm)
Year:	1990
GLP:	yes
Results:	All animals survived the duration of the study at all concentrations tested.
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997)[2]. Meets generally accepted scientific standards and is described in sufficient detail.

Summary details:

This study was designed to assess the toxic effects of TMXDI when administered by inhalation as a vapor to groups of rats and mice. During non-exposure periods, water and food were available to the animals ad libitum. Food and water were withheld during exposures. Each group, (10/sex), was exposed for 6 hours per day, five days per week, for thirteen weeks at target concentrations of 0.4, 0.8 and 1.6 ppm. Temperature and relative humidity measurements were generally recorded 12 times per exposure. Cage placement within the exposure chamber was changed weekly in a predetermined manner to compensate for any possible variations in chamber exposure conditions.

Vapor was generated from a metered syringe pump connected to an electrically heated, vertical glass evaporator. Material passed through the evaporator facilitated by heated compressed air. The evaporator temperature was maintained at a specific range to vaporize the material. Gravimetric analysis was conducted to ascertain if any aerosol was being inadvertently generated. There was no indication of aerosol being present. Particle size distribution was measured 3 times during week 1 and once a week thereafter (except week 4). No mass distribution was calculated since there was no indication of aerosol being generated. Exposure levels were monitored 3x per day by HPLC.

During exposure, physical observations for abnormal signs were recorded on a group basis. Preceding and following each exposure observations were recorded individually. Prior to the first exposure and following exposure the eyes of all rats and mice were examined ophthalmically. All animals were weighed prior to first exposure and then once weekly thereafter. Serum chemistry and hematological evaluations were performed on blood from all surviving rats and mice. Urinalysis was performed on urine of all surviving animals at end of study. Necropsy and histopathology was performed on all animals on the study. The brain, liver, kidneys, lungs, and adrenal glands from all surviving animals and the testes from all male animals were weighed at necropsy and statistically compared to those of control animals.

During non-exposure animals received food and water ad libitum. Room temperature (20±2°C) was monitored and recorded twice daily. Relative humidity was maintained between 32-72%, monitored and recorded twice daily. During exposure the daily mean chamber temperature and relative humidity ranged from 18.5 to 28.9°C and 24.9-59.1%, respectively.

The cumulative mean analytical exposure concentrations as determined by HPLC were 0.00, 0.31, 0.72 and 1.46 ppm of TMXDI vapor.

Three male rats, 10 male mice, and 11 female mice were found dead during the study.

Exposure-related clinical signs were observed in both species of animals. For rats, respiratory difficulties, e.g. gasping, audible respiration, etc, were primarily observed in the 1.6 ppm group with a few animals in the 0.8 ppm group also exhibiting these signs. Reddening of the ears and paws which occurred in all vapor-related groups was most noticeable during exposure and appeared to be concentration related. Reddened ears and paws were still present in some animals on the morning following approximately 18 hours without exposure. Similar signs were observed in mice. Blepharospasm and alopecia were also observed in mice of the 0.8 and 1.6 ppm groups. The alopecia was prominent during the first several weeks of exposure and in some cases resulted in nearly total hair loss. However, the mice did regenerate new hair during the remainder of the study. The incidence of mortality was 5%, 20% and 80% for the 0.4, 0.8, and 1.6 ppm groups, respectively.

Effects on body weight gain for both species were generally concentration related, being depressed for the 1.6 ppm group and being sporadically depressed for the 0.8 and 0.4 ppm groups.

Many of the hematology and serum chemistry parameters were abnormal for rats of the 1.6 ppm group, probably because of their generally debilitated condition. Changes in hematology, serum chemistry, and urinalysis noted for male or female rats of the 0.4 and 0.8 ppm groups were an increased mean corpuscular volume, increased erythrocyte count, decreased albumin concentration, decreased glucose concentration, and decreased urine volume. No concentration-related changes in hematology, serum chemistry, or urinalysis were observed in mice exposed to 0.4 or 0.8 ppm.

At necropsy, the principal observations for rats of the 1.6 ppm group which either died or were humanely killed at week 14 included a color change of the lungs (congestion) and emphysematous lungs. For mice who died, pulmonary congestion and alopecia were the principal observations. The lung was the only organ for which biologically significant organ weight changes occurred. Absolute and/or relative (to either body or brain weight) lung weight values were increased for rats of the 1.6 ppm group and female mice (not statistically significant) of the 0.8 ppm group. For rats and mice which died on study, histopathologic lesions generally occurred throughout the entire respiratory tract. In the nasal cavity the lesions included necrosis, ulceration, squamous metaplasia, and inflammatory changes; necrosis and inflammatory changes generally occurred in the larynx and trachea; pulmonary changes included congestion, hemorrhage, necrosis, inflammation and in several animals, bronchiolar submucosal fibrosis.

In conclusion, mice and rats exposed to vapor TMXDI for up to 13 complete weeks had evidence of toxicity at all exposure concentrations. A no-observable-effect-level was not established for either species, although the incidence, severity, and depth of histologic lesions within the respiratory tract generally decreased with decreasing exposure concentrations.

Note: The following reproductive tissues were examined at necropsy with lesions as noted. There were no significant lesions noted that could be attributed to exposure to TMXDI.

Female mice: Cervix, vagina, ovaries (0.8 ppm: 2 mm clear cysts, bilateral), vulva, oviduct, ureter, uterus (control: bilateral dilatation/distention), mammary glands
Male mice: Prostate, testes, penis, mammary gland, epididymides, ureter, coagulating gland, seminal vesicle
Female rats: Cervix, vagina, ovaries, vulva, oviduct, ureter, uterus, mammary glands
Male rats: Prostate, testes (control: size decrease, bilateral, ½ of normal), penis, mammary gland, epididymides, ureter, coagulating gland, seminal vesicle

References:

[1]Bushy Run Research Center Report # 51-579 for American Cyanamid Company, 1990.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.
See Listing of Codes, p. 59.

3. DEVELOPMENTAL TOXICITY

No Data Found

4. REPRODUCTIVE TOXICITY

Based on the results of the 90-day repeat dose inhalation study there were no macro or microscopic changes in any of the male or female reproductive organs that could be attributed to exposure to TMXDI. Thus suggestive that at the doses tested the material would not be a reproductive toxicant. Based on this it is estimated that this material would not be a reproductive toxicant.

5. GENETIC TOXICITY

A. GENE MUTATIONS[1]

Test Substance:	Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 (In acetone)
Method:	Standard Ames Protocol
Type:	Salmonella typhimurium reverse mutation assay
System of testing:	TA-98, TA-100, TA-1535, TA-1537 and TA-1538
Concentrations:	0.1, 1, 10, 100 µg/plate (0.1 µL test substance/plate)
Controls:	Yes, Positive controls = 2-aminoanthracene (2-AA), 4-nitro-o-phenylenediamine (4-NPD), 9-aminoacridine (9-AA), and sodium azide (NaN_3) Negative controls = acetone solvent control
Cytotoxic conc.:	100 – 10,000 µg/plate
Metabolic activation:	with and without Aroclor induced rat liver S-9 (50 µl/plate S-9 preparation)
Year:	1986
GLP:	Yes
Result:	non-mutagenic
Remark:	This study is assigned a reliability code of 1d according to the criteria established by Klimisch *et al.* (1997)[2]. Meets generally accepted scientific standards and is described in sufficient detail.

Summary details:

Isocyanic acid, m-phenylenediiso-propylidene (TMXDI) was non-mutagenic in the Ames Salmonella Plate Assay with and without metabolic activation (S-9) using bacterial strains TA-98, TA-100, TA-1535, TA-1537, and TA-1538.

Test article was prepared by mixing TMXDI in acetone to achieve a concentration of 6 mg/ml. Desired test concentrations were obtained by serial dilution. A preliminary toxicity test was performed using TA-100 to determine the level of toxicity of the test substance. Ten doses were tested for toxicity with a plate assay performed in the manner used for mutagenicity determinations. Toxicity was assessed at 24 to 48 hours after treatment by observations for

either growth inhibition of the background lawn or a reduction in the number of spontaneous mutants. The maximum concentration tested was 10,000 µg/plate. Dose levels ranging from 100 µg/plate to 10,000 µg/plate were cytotoxic. A dose of 30 µg/plate allowed only sparse growth of the background lawn. The lower doses tested (1 – 10 µg/plate) did not inhibit growth of the bacteria. Based on these results, 5 doses ranging from 0.3 µg/plate to 30 µg/plate were selected for the definitive assay. The assay was repeated using TMXDI concentrations of 0.3, 1, 3, 10, and 30 µg/plate. No evidence of base-pair substitution or frame-shift mutation was seen.

Strain	Substance	Concentration tested	Number of Colonies/Plate	
		µg/plate	Mean w/o S-9	Mean w/ S-9
TA-98	TMXDI	30	41	30
		10	42	25
		3	28	19
		1	19	21
		0.3	12	29
	4-NPD	10	1239	
	2-AA	10		2418
	Acetone	40,000	33	21
TA-100	TMXDI	30	106	S
		10	96	103
		3	114	100
		1	109	118
		0.3	132	101
	NaN_3	10	1507	
	2-AA	10		1877
	Acetone	40,000	100	115
TA-1535	TMXDI	30	23	14
		10	24	11
		3	24	9
		1	26	15
		0.3	25	6
	NaN_3	10	1686	
	2-AA	10		107
	Acetone	40,000	25	14

TA-1537	TMXDI	30	4	2(T)
		10	5	7
		3	7	9
		1	7	7
		0.3	12	8
	9-AA	60	93	
	2-AA	10		598
	Acetone	40,000	7	8
TA-1538	TMXDI	30	S	16
		10	13	15
		3	4	17
		1	8	15
		0.3	7	16
	4-NPD	10	1267	
	2-AA	10		1112
	Acetone	40,000	5	14

S= Sparse growth of background lawn; counts not included in calculation of mean and standard deviation.
T= Toxic to background lawn.

References:

[1]Ames Bacterial/Microsome Mutagenicity Tests of TMXDI by Bushy Run Research Center for American Cyanamid Company, May 6, 1986.

[2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997. See Listing of Codes, p. 59.

B. CHROMOSOMAL ABERRATIONS

No Data Found

J. GENERAL REFERENCE

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.

1 = Valid without restriction

1a: GLP guideline study
1b: Comparable to guideline study
1c: Meets national standard methods (AFNOR/DIN)
1d: Meets generally accepted scientific standards and is described in sufficient detail

2 = Valid with restriction

2a: Guideline study without detailed documentation
2b: Guideline study with acceptable restrictions
2c: Comparable to guideline study with acceptable restrictions
2d: Meets national standard methods with acceptable restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
2f: Accepted calculation method
2g: Data from Handbook or collection of data

3 = Invalid

3a: Documentation insufficient for assessment
3b: Significant methodological deficiencies
3c: Unsuitable test system

4 = Not assignable

4a: Abstract
4b: Secondary literature
4c: Original reference not yet available
4d: Original reference in foreign language
4e: Documentation insufficient for assessment.