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CAS 100-00-5 1 OF 1

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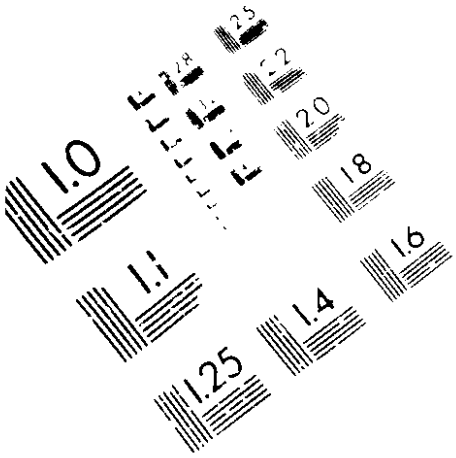

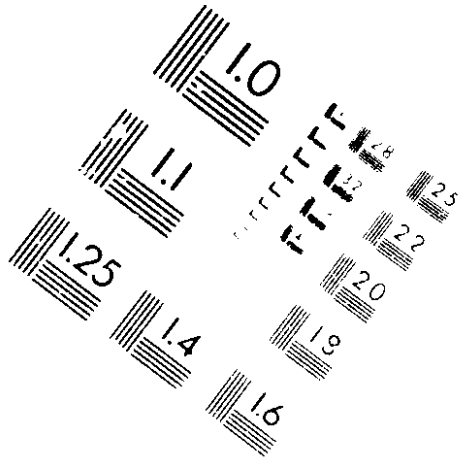

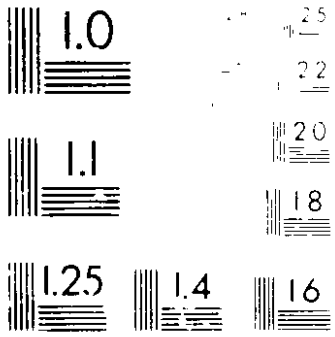

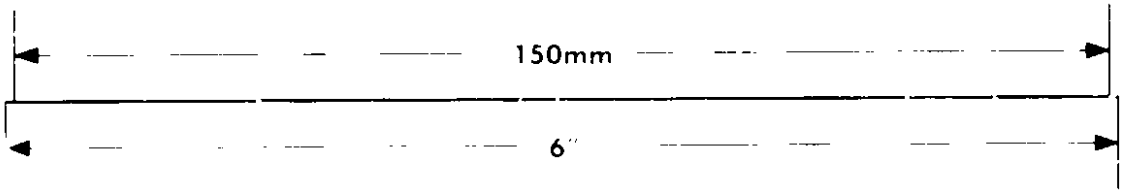

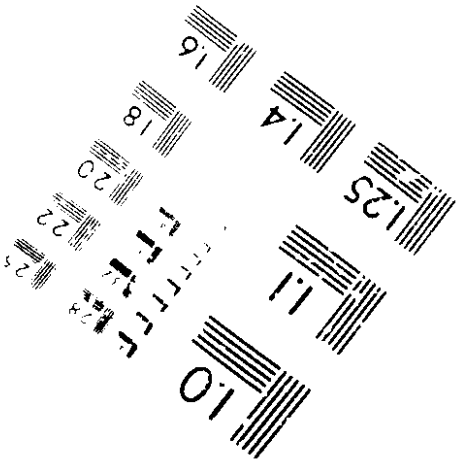

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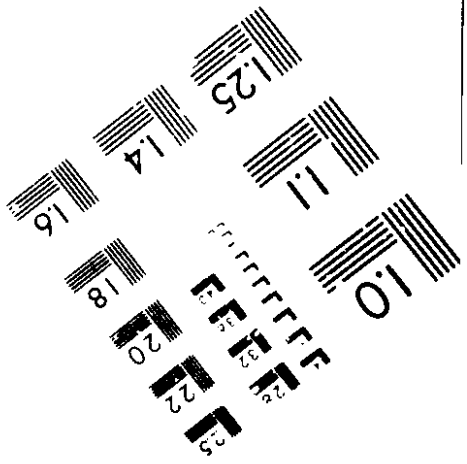

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MUTAGENIC ACTIVITY OF PARA-CHLORONITROBENZENE IN THE SALMONELLA/MICROSOME ASSAY WITH COVER LETTER OUTLINING CURRENT STUDY OF TETRAHYDROFURAN DATED 05/10/94 (SANITIZED)		
Chemical Category		
PARA-CHLORONITROBENZENE (100-00 5)		

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Environmental Protection Agency
401 M Street SW
Washington, DC 20460
Attention: 8(d) Reporting

Dear Sir/Madam:

OPPTS-82042; FRL-4745-5

In response to the subject final rule published in the Federal Register on February 9, 1994 (59FR 5956, and effective on March 11, 1994, DuPont Specialty Chemicals submits the enclosed toxicity reports under TSCA section 8(d) Health and Safety Data Reporting on the following chemicals: Dimethyl sulfate, p-Chloronitrobenzene , m-Toluidine, 1,3-Dinitrobenzene, Diphenylamine, , 2,4 - Dinitrotoluene, o-Anisidine, Chlorobenzene, Tetrahydrofuran, o-Nitrotoluene, Xylidine, p-Nitroaniline and Phenylhydrazine.

Additionally, we are aware of the following ongoing studies on Tetrahydrofuran (THF).

Under a TSCA section 4 (a) test rule THF is being evaluated for neurotoxicity potential. The testing is being conducted by DuPont on behalf of an industry consortium, the THF Task Force umbrellaed under the Synthetic Organic Chemical Manufacturers Association (SOCMA). To date the in-life phase of an acute neurotoxicity study has been completed. Subchronic neurotoxicity testing including neuropathology and evaluations for Motor Activity and Functional Observation Battery will be conducted in the near future.

A two-generation reproduction toxicity study is underway at BASF's toxicology laboratories in Germany to determine the reproductive toxicity potential of THF through the oral route of exposure (compound administered in drinking water) The in-life phase of the one generation rangefinder (for the main study) has been completed. The main study is expected to begin later this year. The studies are being conducted by BASF on behalf of an industry consortium of which DuPont is a member

Final reports from both studies will be submitted to EPA when they issue. the final report from the reproductive toxicity rangefinder has been submitted to EPA under the 8(d) rule by BASF.

You may contact me on 302/774-6467 if there are any questions regarding this submission.

Yours truly,

KDDastur

K. D. Dastur
Manager, Product Toxicology
and Chemical Regulations

/pmt
Enclosure

86940000761

LIST OF SUBMITTED STUDIES

Title	Report #
Dimethyl Sulfate (CAS #77-78-1)	
1. Industrial Hygiene Survey of DMS Manufacture and Use- (CBI) Plant	HLR# 203-77
2. Industrial Hygiene Survey of DMS Manufacturing Facilities - (CBI) Plant	HLR# 202-77
3. Acute Inhalation Toxicity and Antidote Study	HLR# 318-71
4. Preliminary Tests on the Toxicity of Diethyl Sulfate and Diethyl Peroxide (DMS data included)	NA
5. Primary Skin Irritation and Sensitization Tests on Guinea Pigs	HLR# 22-72
6. Mutagenicity Evaluation in Salmonella Typhimurium	HLR# 348-81
7. Dimethyl Sulfate Permeation Testing	HLR# 261-81
8. Dimethyl Sulfate Permeation Testing	HLR# 538-81
9. Teratogenicity Study of Dimethyl Sulfate in Rats	HLR# 535-91
10. Carcinogenicity and Chronic Toxicity of Inhaled Dimethyl Sulfate	NA
1-Chloro-4-nitrobenzene (p-Nitrochlorobenzene) (CAS#100-00-5)	
1. Inhalation Median Lethal Concentration (LC50)	HLR# 751-81
2. Subchronic Inhalation Toxicity Study of p-Chloronitrobenzene (PCNB) in Rats	HLR# 429-84
3. 96-Hour LC50 to Fathead Minnows	HLR#62-79
4. Toxicity of Compounds Used in (CBI) Building	HLR# 13-49
5. Eye Irritation Test in Rabbits	HLR# 57-82
6. In Vitro Microbial Mutagenicity Studies of p-Nitrochlorobenzene	HLR# 404-75
7 Mutagenic Activity of Mixed Nitrochlorobenzene [o-, p-] in the Salmonella Microsome Assay	HLR# 539-77
8 Mutagenic Activity of para-Chloronitrobenzene In Salmonella/Microsome Assay	HLR# 538-77
9. Mutagenic Activity of Benzene, para-Nitrochloro-46.5% in Salmonella/Microsome Assay	HLR# 965-77
10. Mutagenic Activity of Mixed Nitrochlorobenzene in Salmonella/Microsome Assay	HLR# 964-77
11. Mutagenic Activity in the Salmonella/Microsome Assay	HLR# 392-78
12. Mutagenic Activity in the Salmonella/Microsome Assay	HLR# 535-78
13. Mutagenic Activity in the Salmonella/Microsome Assay	HLR# 536-78
14. Mutagenic Activity in the Salmonella/Microsome Assay	HLR# 705-78
15. Mutagenic Activity in the Salmonella/Microsome Assay	HLR# 275-79
16. Mutagenic Activity in the Chinese Hamster Ovary Assay	HLR# 24-80

List of Submitted Studies (continued)

Title	Report #
1,3-Dinitrobenzene (CAS#99-65-0)	
1. Nitrobenzene Derivatives	NA
Diphenylamine (CAS#122-39-4)	
1. Para Chlor Aniline Quinaldine and (CBI)	NA
2. Results of Inorganic Lead and Diphenylamine Air Samples Collected at the (CBI) Plant	HLR# 484-76
3. Department of Transportation Skin Corrosion Test on Rabbit Skin	HLR# 421-75
2,4, - Dinitrotoluene (CAS#121-14-2)	
1. Industrial Hygiene Survey of the (CBI) Involving Dry Chemical Handling Procedures	HLR# 71-77
2. Evaluation of Exposure to 2,4-Dinitrotoluene While Handloading Shotshell - (CBI)	HLR# 654-79
3. Class B Poison Labelling Test	HLR# 26-66
4. 96-Hour LC50 to Fathead Minnows	HLR# 61-79
5. Eye Irritation Test in Rabbits	HLR# 713-81
6. Department of Transportation Skin Corrosion Test on Rabbit Skin	HLR# 556-73
7. Oral Bioassay Study (Dogs)	HLR# 490-76
8. The Toxicity of TNT and DNT	NA
9. Teratological and Postnatal Evaluation of Dinitrotoluene in Fischer 344 Rats	RTI Report RTI/1938/0003F
10 A thirty day toxicology study in Fischer 344 rats given dinitrotoluene-technical grade. (Study performed at Hazleton Laboratories America, Inc. for Chemical Industry Institute of Toxicology, Research Triangle Park, NC-	

List of Submitted Studies (Continued)

Title	Report #
o-Anisidine (CAS#90-04-0)	
1. Toxicity of Compounds Used in (Hydrogen Reduction) Building	NA
2. Department of Transportation Skin Corrosion Test on Rabbit Skin	HLR# 532-73
3. In Vitro Microbial Mutagenicity Studies of ortho-Anisidine	HLR# 247-75
4. Toxic Hazards Evaluation of Five Atmospheric Pollutants from Army Ammunition Plants	NA
Chlorobenzene (CAS#108-90-7)	
1. Mutagenic Acitivty of Monochlorobenzene in the Salmonella/Microsome Assay	HLR# 537-77
Tetrahydrofuran (CAS#109-99-9)	
1. Acute Toxicity Evaluation By Aspiration and Insufflation	HLR# 374-71
2. Toxicity of Tetrahydrofuran	NA
3. Acute Inhalation Toxicity in Rats	HLR# 848-79
4. 48-Hour LC50 to Daphnia Magna	HLR# 744-80
5. 96-Hour LC50 to Fathead Minnows	HLR# 745-80
6. Federal Hazardous Substances Act Test - Rabbit Eye Irritation	HLR# 290-71
7 96-Hour LC50 to Fathead Minnows	HLR# 135-82
8. Tetrahydrofuran (THF) Inhalation Effect on the Rat Conceptus	HLR# 750-82
o-Nitrotoluene (CAS#88-72-2)	
1 Inhalation Class B Poison	HLR# 98-72
2. Class B Poison Tests on Rabbit Skin	HLR# 84-72
3. Acute Oral Test	HLR# 56-72
4 Department of Transportation Skin Irritation Test on Rabbit Skin	HLR#626-73
Phenylhydrazine (CAS#100-63-0)	
1 Acute Skin Absorption Toxicity	HLR# 106-63

List of Submitted Studies (Continued)

	Title	Report #
Xylidine (CAS#1300-73-8)		
1	Class B Poison Test	HLR# 228-69
2.	Class B Poison Test	HLR# 172-69
3.	Department of Transportation Skin Corrosion Test on Rabbit Skin	HLR# 538-73
4-Nitroaniline (p-Nitroaniline) (CAS#100-01-6)		
1.	Subchronic Inhalation Toxicity Study of p-Nitroaniline (PNA) in Rats	HLR# 372-84
2.	Toxicity of Compounds Used in Hydrogen Reduction Building	NA
3	Inhalation Median Lethal Concentration (LC50)	HLR# 856-81
4	Micronucleus assay with p-Nitroaniline	MSL-9283
m-Toluidine (CAS#108-44-1)		
1.	Oral Class B Poison Test	HLR# 543-74
2.	Oral LD50 Test in Rats	HLR# 955-80
3.	Eye Irritation Test in Rabbits	HLR# 945-80
4	Skin Irritation Test in Rabbits	HLR# 948-80
5.	DOT Skin Corrosion Test	HLR# 527-73

SPEC CONTROL

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[CBI]

E. I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine

HASKELL LABORATORY REPORT NO. 576-77 MR NO. [CBI]

Material Tested: para-Chloronitrobenzene Haskell No. 11,258

Material Submitted By: [CBI] Sample Ready for Testing: 5-[illegible]-77
Other Code: [CBI]

MUTAGENIC ACTIVITY OF para-CHLORONITROBENZENE
IN THE *SALMONELLA/MICROSOME ASSAY*

Materials and Methods: Five histidine-requiring strains of *Salmonella typhimurium* were used in the mutagenicity assays. Strains TA 1535 and TA 100 are used to detect base-pair substitution mutations, whereas strains TA 1537, TA 1538 and TA 98 are used to detect frame-shift mutations. (Ames, McCann and Yamasaki, Mutation Research 31 (1975) 347-364)

The tests were performed in the presence and absence of a rat-liver homogenate activation system (S-9). In the absence of metabolic activation, 0.1 ml of a solution of the test compound and approximately 10^8 bacteria were added to 2 ml of top agar (0.6% agar, 0.6% NaCl, 0.05 mM L-histidine, 0.05 mM biotin). The solution was mixed and poured onto the surface of a Davis minimal agar plate. The metabolic activation system involved the addition of 0.5 ml of S-9 mix to the chemical-top agar solution. The S-9 mix contains per ml: 0.3 ml of the 9,000 X g supernatant of homogenized liver, 8 mM $MgCl_2$, 33 mM KCl, 5 mM glucose-6-phosphate, 4 mM NADP and 100 mM sodium phosphate (pH 7.4). This mixture was added directly to the top agar immediately before it was poured over the minimal agar plate.

Prior to testing for mutagenicity, the compound was tested for toxicity to the tester strains.

Appropriate controls were included for each strain. In the nonactivated system these controls consisted of a negative, or solvent control, and positive controls. A second negative control (-S-9 control) is included in the activated assay to measure any activity of the compound in the absence of the S-9 activator mixture.

All plates were incubated at 37°C for 48 hours.

Results: Tables I, II, and III.

Summary: para-Chloronitrobenzene was tested in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 in concentrations up to 3000 µg per petri plate. The compound is considered weakly-mutagenic based entirely on the demonstration of a positive dose response in two trials with a 4.1-fold induced increase over the spontaneous mutation frequency in the most active strain - TA 1535 with metabolic activation. The calculations gave a mutation frequence of only 0.003 revertants per µmole for this pure compound. A weak mutagen is defined as giving a 2-3 fold increase over the spontaneous frequency or between 0.02 to 0.1 revertants per µmole.

Report by: James F. Russell, Jr.
James F. Russell, Jr.
Molecular Biologist

Approved by: David F. Krahn
David F. Krahn
Chief, Molecular Biology Section

JFR:DFK:ms

Date: July 13, 1977

Notebook No. [CBI]

TABLE 1

MUTAGENIC ACTIVITY OF para-CHLOPONITROBENZENE IN *SALMONELLA TYPHIMURIUM* STRAINS TA 1535, TA 1537, TA 1538, TA 98 AND TA 100 WITH METABOLIC ACTIVATION

(Trial #1)

Compound Added			Histidine+ Revertants Per Plate**				
			TA 1535	TA 1537	TA 1538	TA 98	TA 100
DMSO			10	7	16	26	[illegible]
-S-9* (500 µg/plate)			18	5	8	[illegible]	[illegible]
11,258	600	µg/plate	22	4	16	28	[illegible]
	1200	"	37	8	18	17	[illegible]
	1800	"	41	5	[illegible]	22	[illegible]
	2400	"	29	4	7	13	[illegible]
	3000	"	30	4	7	19	[illegible]
2AA	5	"					[illegible]
	10	"	262		1784	[illegible]	
	100	"		346			

DMSO = Dimethylsulfoxide (solvent control)

11,258 = para-Chloronitrobenzene

2AA = 2-Aminoanthracene (positive control)

* = Test plate without S-9 and activators

** = Average of two plates

TABLE II

MUTAGENIC ACTIVITY OF para-CHLORONITROBENZENE IN *SALMONELLA TYPHIMURIUM* STRAINS TA 1535 AND TA 100 WITH METABOLIC ACTIVATION

(Trial #2)

Compound Added		Histidine+ Revertants Per Plate**	
		TA 1535	TA 100
DMSO		20	146
-S·9*	(500 µg/plate)	18	115
II,258	400 µg/plate	26	265
	800 "	40	267
	1200 "	48	308
	1600 "	30	291
	2000 "	47	308
2AA	5 "		2083
	10 "	333	

DMSO = Dimethylsulfoxide (solvent control)

II,258 = para-Chloronitrobenzene

2AA = 2-Aminoanthracene (positive control)

* = Test plate without S·9 and activators

** = Average of two plates

TABLE III

MUTAGENIC ACTIVITY OF para-CHLORONITROBENZENE IN *SALMONELLA TYPHIMURIUM* STRAINS TA 1535, TA 1537, TA 1538, TA 98 AND TA 100 WITHOUT METABOLIC ACTIVATION

Compound Added		Histidine$^+$ Revertants Per Plate*				
		TA 1535	TA 1537	TA 1538	TA 98	[illegible]
DMSO		18	8	14	16	[illegible]
11,258	100 µg/plate	14	7	12	22	[illegible]
	200 "	20	9	14	5	[illegible]
	300 "	21	7	19	4	
	400 "	19	7	15	9	[illegible]
	500 "	23	6	16	15	[illegible]
MNNG	2 "	848				
9AAc	50 "		980			
2NF	25 "			1578	1545	

DMSO = Dimethylsulfoxide (solvent control)

11,258 = para-Chloronitrobenzene

MNNG = N-Methyl-N'-Nitro-N-Nitrosoguanidine (positive control)

9AAc = 9-Aminoacridine (positive control)

2NF = 2-Nitrofluorene (positive control)

* = Average of two plates

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