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CAS 100-00-5 1 OF 1

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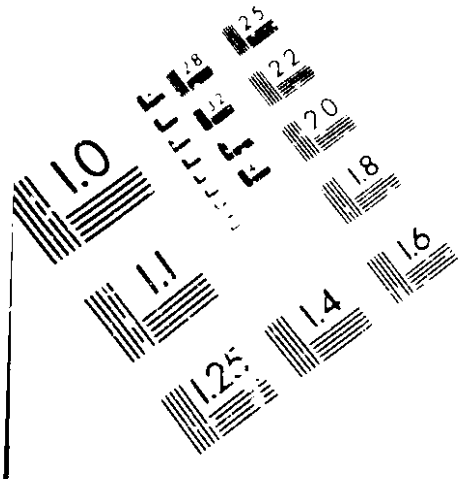

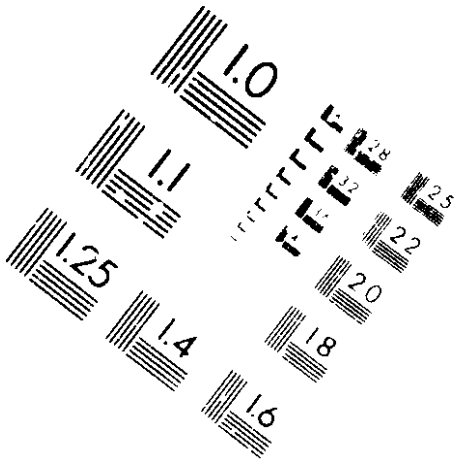

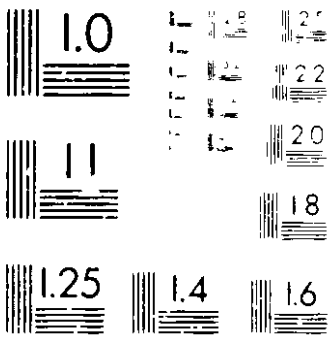

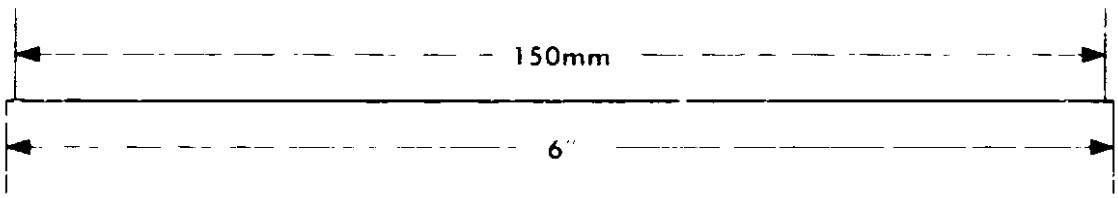

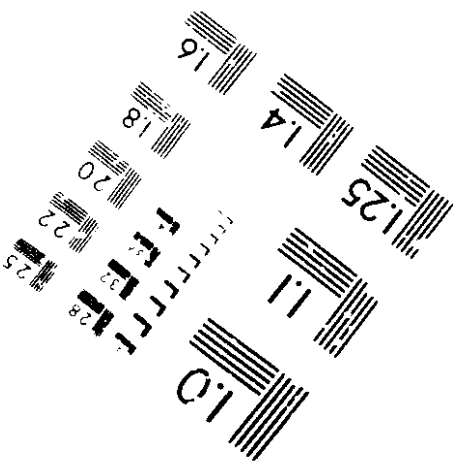

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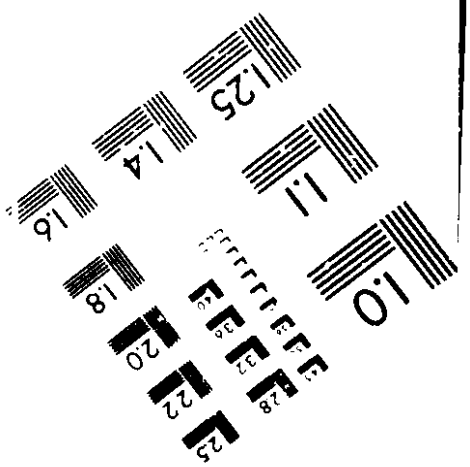

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MUTAGENIC ACTIVITY IN THE SALMONELLA/MICROSOME ASSAY OF 1-CHLORO-4-NITRO- [] W/COVER LETTER OUTLINING CURRENT STUDY OF TETRAHYDROFURAN TOXICITY DATED 05/10/94 (SANITIZED)		
Chemical Category		
BENZENE, 1-CHLORO-4-NITRO- (100 00-5)		

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May 10, 1994

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Office of Pollution Prevention and Toxics
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Attention: 8(d) Reporting

Dear Sir/Madam:

OPPTS-32042; 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# 31[illegible]-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
Tetranydrofuran (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#10[illegible]3-[illegible]	
1 Acute Skin Absorption Toxicity	HLR# 106-83

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

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DU PONT CONFIDENTIAL

[CBI]

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

HASKELL LABORATORY REPORT NO. 536-78 MR NO. [CBI]

Material Tested: Benzene, 1-chloro-4-nitro- (see page 2 for composition)

Haskell No. 12,479-0
Other Code: [CBI]

Material Submitted by: [CBI]

Sample Ready for Testing: 8-16-78

MUTAGENIC ACTIVITY IN THE *SALMONELLA*/MICROSOME ASSAY

Materials and Methods: The ability of the test sample to revert five strains of *Salmonella typhimurium* from histidine dependence to histidine independence is determined. Strains TA 1535 and TA 100 are used to detect base-pair substitution mutations, whereas TA 1537, TA 1538, and TA 98 are used to detect frame-shift mutations.[1]

The assay is performed in the presence and the absence of a rat-liver homogenate activation system. In the absence of an activation system, 0.1 ml of a solution of the test sample and approximately 10^8 bacteria in 0.1 ml are added to 2 ml of top agar (0.6% agar, 0.6% NaCl, 0.05 mM L-histidine, 0.05 mM biotin). These components are mixed and poured on the surface of a plate containing 20 ml of Davis minimal agar. To treat in the presence of an activation system, 0.5 ml of S-9 is added to the bacteria-test sample-top agar mixture. S-9 is the 9,000 x g supernatant of liver homogenate from rats given 500 mg of Aroclor 1254/kg five days before sacrifice. The S-9 mix contains per ml: 0.3 ml of S-9, 8 mM $MgCl_2$, 33 mM KCl, 5 mM glucose-6-phosphate, 4 mM NADP and 100 mM sodium phosphate (pH 7.4). The S-9 mix is added to the bacteria test sample and top agar. These components are mixed and immediately poured over the minimal agar plate. The revertant colonies are counted after the plates are incubated at 37° for 48 hr.[1]

Positive (known mutagens) and negative (solvent) controls are included in each assay.

[1] Ames, McCann and Yamasaki, Mutation Res. 31: 347-364, 1975.

The cytotoxicity of the test sample in the presence and absence of an activation system, as measured in strain TA 1535, is the basis for selecting concentrations to be used in the mutagenesis experiment. The protocol used to determine the cytotoxicity is identical to the mutagenesis protocol except that 10^3 rather than 10^8 bacteria are used per plate and a nonlimiting concentration of histidine is present. Concentrations of test sample that are nontoxic and, if possible, slightly toxic are selected for the mutagenesis assay.

The data are handled as follows: Data from replicate plates within a single experiment are averaged. The average of these values from different experiments is determined. The highest average number of revertants that is obtained is expressed as a multiple of the control value for the sensitive strain(s). When a test sample is active, the average numbers of revertants observed before activity plateaus or decreases at the various concentrations tested are submitted to linear regression analysis. The slope of the line thus obtained is used to determine the number of revertants/nmole or µg of test sample.

Results: On the basis of the initial cytotoxicity experiment with strain TA 1535, nontoxic and slightly toxic concentrations of Benzene, 1-chloro-4-nitro- were chosen for the mutagenesis experiment. Concentrations were reduced in Trial 2 in the presence of the activation system in order to demonstrate a dose-response relationship.

The mutagenesis data are listed in Tables I and II for Trial 1 and in Tables III and IV for Trial 2.

Summary: Benzene, 1-chloro-4-nitro- was tested in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100. This chemical is mutagenic for strain TA 1535 in the presence of an activation system and weakly mutagenic for strain TA 100 in the presence of an activation system in experiments performed by the described protocol.

The mutagenic activity is as follows:

With Activation:	TA 1535	4.3-4.8 times the spontaneous revertant frequency (.01 rev/nM)
	TA 100	2.9-3.0 times the spontaneous revertant frequency (.05-.08 rev/nM)

Composition: [CBI]

Report by: Maureen E. Suppel
Maureen E. Suppel
Molecular Biologist

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

Notebook No. [CBI]
MES:DFK:ms
Report No. 536-78
Date: September 29, 1978

TABLE I

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

Trial I

Compound Added			Histidine[1] Revertants Per Plate*				
			TA 1535	TA 1537	TA 1538	TA 98	TA 100
DMSO			19	10	25	26	143
12,479-02		µg/plate					
"	500	"	67	9	21	39	410
"	1000	"	86	8	23	38	417
"	2500	"	91	5	18	29	387
"	5000	"	92	3	19	21	269
"	10000	"	85	1	12	6	246
2AA	5	"					298
"	10	"	362		12[illegible]	1514	
"	100	"		201			

DMSO = Dimethylsulfoxide (solvent control)

12,479-02 = Benzene, 1-chloro-4-nitro-

2AA = 2-Aminoanthracene (positive control)

* = Average of 2 plates

TABLE II

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

Trial I

Compound Added			Histidine+ Revertants Per Plate*				
			TA 1535	TA 1537	TA 1538	TA 98	TA 100
DMSO			31	9	14	23	149
12,479-02	µg/plate						
"	100	"	40	10	14	19	134
"	250	"	34	9	16	29	136
"	500	"	42	7	17	19	168
"	1000	"	55	6	9	18	158
"	2500	"	51	6	14	19T	134T
MNNG	2	"	1262				2372
9AAc	50	"		489			
2NF	25	"			1826	2369	

DMSO = Dimethylsulfoxide (solvent control)
12,479-02 = Benzene, 1-chloro-4-nitro-
MNNG = N-Methyl-N'-nitro-N-nitrosoguanidine (positive control)
9AAc = 9-Aminoacridine (positive control)
2NF = 2-Nitrofluorene (positive control)
* = Average of 2 plates
T = Toxicity indicated by decreased density of the background lawn

TABLE III

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

Trial 2

Compound Added			Histidine$^+$ Revertants Per Plate*				
			TA 1535	TA 1537	TA 1538	TA 98	TA 100
DMSO			23	12	35	43	159
12,479-02		µg/plate					
"	250	"	62	15	38	42	231
"	500	"	76	15	26	43	405
"	1000	"	98	11	33	31	476
"	2500	"	93	16	26	34	314
"	5000	"	92	11	21	30	285T
2AA	5	"					1529
"	10	"	477		1119	1692	
"	100	"		319			

DMSO = Dimethylsulfoxide (solvent control)
12,479-02 = Benzene, 1-chloro-4-nitro-
2AA = 2-Aminoanthracene (positive control)
* = Average of 2 plates
T = Toxicity indicated by decreased density of the background lawn

TABLE IV

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

Trial 2

Compound Added			Histidine+ Revertants Per Plate*				
			TA 1535	TA 1537	TA 1538	TA 98	TA 100
DMSO			46	13	13	18	140
12,479-02		µg/plate					
"	100	"	34	13	18	25	137
"	250	"	42	11	10	17	129
"	500	"	49	11	18	18	153
"	1000	"	63	10	10	16	150
"	2500	"	47	7	12	13T	112T
MNNG	2	"	2368				1897
9AAc	50	"		630			
2NF	25	"			1773	1997	

DMSO = Dimethylsulfoxide (solvent control)
12,479-02 = Benzene, 1-chloro-4-nitro-
MNNG = N-Methyl-N'-nitro-N-nitrosoguanidine (positive control)
9AAc = 9-Aminoacridine (positive control)
2NF = 2-Nitrofluorene (positive control)
* = Average of 2 plates
T = Toxicity indicated by decreased density of the background lawn

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