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TITLE:

ACUTE INHALATION TOXICITY STUDY OF
N,N-DIMETHYL-P-TOLUIDINE IN RATS

Study Director:
Inhalation Toxicologist

Aerosol Scientist:

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Prepared By:

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8697000014
869700001143

Prepared For:

First Chemical Corporation
P.O. Box 1427
Pascagoula, MS 39568

Sponsor's Representative:

CSRAD/OPPT

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mb

SUMMARY

The test substance, N,N-Dimethyl-p-Toluidine (DMPT), was aerosolized and administered for 4-hr by whole-body inhalation exposure to four treatment groups, each consisting of five male and five female Sprague-Dawley-derived rats. Animals were initially exposed to a target concentration of 5 mg/l. Target concentrations for the three subsequent exposures were selected based on mortality due to this initial exposure and the results of each subsequent exposure. For the four DMPT exposures included in this study, the test atmosphere concentrations, as determined by chemical analysis of the combined aerosol and vapor phases using filter- and impinger-collected samples, were 5.27, 1.73, 0.99, and 0.30 mg/l. Aerosol particle size ranged from 0.23 to 0.57 μm Mass Median Aerodynamic Diameter (MMAD). Exposure of the animals was followed by a 14-day observation period. No rats survived a 4-hour exposure to 5.27 mg/l. Exposure to 0.30 or 0.99 mg/l produced no mortality, while exposure to 1.73 mg/l produced 60% mortality in male rats and 100% mortality in female rats. Using these data, the median lethal concentration (LC_{50}) was estimated to be about 1.4 mg/l. Clinical signs in rats exposed to 1.73 mg/l included hypoactivity, a comatose/prostrate condition, dyspnea or rapid respiration and salivation. The most frequently observed signs in rats exposed to 0.99 or 0.30 mg/l were nasal discharge and red material around the nose, but dyspnea was also reported for several rats from the 0.30 mg/l group. For groups in which animals survived, body weight gain was similar between groups of the same sex. Mottled lungs, red ovaries and gas-filled gastrointestinal organs were the most frequent gross lesions in rats exposed to 5.27 or 1.73 mg/l. No gross lesions were observed in rats exposed to lower concentrations.

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II. OBJECTIVE

The objective of this study was to determine the acute toxicity including the median lethal concentration (LC₅₀), of N,N-Dimethyl-p-Toluidine when administered in graduated concentrations by whole-body inhalation exposure to male and female Sprague-Dawley rats.

III. MATERIALS AND METHODS

A. Test Substance:

Identification:	N,N-Dimethyl-p-Toluidine
Primary Ingredient:	N,N-Dimethyl-p-Toluidine - 99%; (Cas No. 99-97-8)
Specific Gravity:	0.93
Boiling Point:	211°C
Melting Point:	Not Applicable
Flash Point:	82°C (Closed Cup)
Vapor Pressure:	5 mm of Hg at 72°C
Solubility in Water (%):	Less than 0.1
Appearance:	Clear colorless liquid

The test substance, N,N-Dimethyl-p-Toluidine, I.D. No. UN 1708, was received November 2, 1992. The test substance was a clear colorless liquid and was stored in the original container at room temperature. Determinations of stability, strength, purity and homogeneity of the bulk test substance and attendant documentation were the responsibility of the Sponsor. All remaining test substance will be returned to the Sponsor.

- B. Inhalation Exposure: Four groups of 5 rats/sex were exposed to test atmospheres of N,N-Dimethyl-p-Toluidine for a single 4-hour period in a 500 liter stainless steel and glass Rochester-type inhalation exposure chamber. Based on preliminary test atmosphere development results, a target concentration of 5 mg/l was used for the initial exposure. Target concentrations for all subsequent exposures were selected based on mortality caused by previous exposure(s). The exposures were conducted on 12/08/92, 12/10/92, 12/16/92 and 01/05/93. Conditioned room air, which was passed through coarse and HEPA filters before entering the exposure chamber, was used as supply air. Chamber exhaust was passed through a HEPA filter. Chamber temperature and relative humidity were monitored with an electronic thermohygrometer (Cole-Parmer Co., Chicago, IL). The chamber airflow rate was monitored continuously with a calibrated differential pressure gauge. Chamber temperature, relative humidity and airflow rate were recorded at approximately 30 min. intervals

during the exposures. The chamber oxygen concentration was measured at least three times during the exposures using a Lynn Model 6200 or Servomex Series 1400 oxygen analyzer (Lynn Products Co., Lynn, MA and Servomex, Inc., Norwood, MA, respectively).

- C. Test Atmosphere Generation: Test atmospheres of N,N-Dimethyl-p-Toluidine were generated by aerosolizing the test substance and appropriately diluting the aerosols with filtered air. The N,N-Dimethyl-p-Toluidine aerosols were generated by a stainless-steel aspirator device (Laskin type) for the two higher exposure concentrations (5.27 and 1.73 mg/l) and a modified commercial nebulizer (DeVilbiss, Model 40, Somerset, PA) for the two lower exposure concentrations (0.99 and 0.30 mg/l).

The Laskin fixture consisted of 1/4-inch diameter stainless-steel tube with two to four orifices spaced evenly around the periphery. At each orifice a 1/16-inch diameter stainless-steel aspirator tube was attached for delivery of the test substance. The test material was delivered from a reservoir to the aspirator (by head pressure and suction) through Teflon tubing and a manifold equipped with a metering valve. The output of the generator was directed against an impaction surface to remove coarse particles and control particle size. Aerosol concentration was maintained at a constant level by adjusting air pressure to the aspirator and delivery rate of the test material.

The DeVilbiss Model 40 nebulizer was modified with the addition of a larger liquid reservoir. Fresh test material was added to the reservoir periodically during the exposure in order to maintain a constant liquid level.

- D. Test Atmosphere Concentration Monitoring: Mass concentration of N,N-Dimethyl-p-Toluidine in the breathing zone of the rats was determined chemically by analyzing filter samples (aerosol phase collection) and impinger samples (vapor phase collection) collected once each hour during the exposure. The sampling train consisted of a pre-weighed filter in series with two mini impingers filled with isopropyl alcohol connected to a constant flow vacuum pump. The filter and impinger samples were analyzed by a gas chromatographic method provided by the Sponsor and modified by [redacted] to quantitatively determine the amount of N,N-Dimethyl-p-Toluidine. A dry-gas meter connected to the positive pressure side of the pump was used to record the corresponding volume of chamber air sampled and the weight to volume ratio was determined. In addition appropriate real-time sensors (aerosol sensor for the two high exposure levels and an infrared vapor sensor for the two low exposure levels) were used to monitor exposure concentrations. These sensors were used only as continuous indicators of short term changes in exposure concentration to guide laboratory personnel in correcting concentration excursions.

- E. Aerosol Particle Size Distribution: Aerosol particle size was monitored with a Quartz Crystal Microbalance cascade impactor (California Measurements, Inc., Sierra Madre, CA).
- F. Animals: Animals for this study were received in two shipments. Animals from the first shipment were used for the first three exposures and those from the second shipment were used for the fourth exposure. Male and female Sprague-Dawley-derived rats were purchased and were received on 12/01/92 (26/sex) and 12/29/92 (15/sex). Approximate dates of birth for these shipments were 10/26/92 (males) and 10/19/92 (females) and 11/23/92 (males and females), respectively. At arrival, the rats were approximately 36-43 days of age. The body weight ranges at arrival were 131-158 g for male rats and 124-143 g for female rats from the first shipment and 130-156 g for male rats and 126-160 g for female rats from the second shipment. The animals were held in quarantine for at least one week before use. All animals appeared healthy and active at receipt and when weighed for group assignment. Therefore, all rats were considered to be suitable for use as test subjects. Rats selected for the study were identified by a uniquely numbered metal tag inserted through the pinna of the right ear and by a cage card. The rats were approximately 43-58 days of age at exposure.
- G. Feed and Water: The NIH-07 open formula pellet diet (Ziegler Bros., Gardners, PA) and water from an automatic watering system were available ad libitum, except during the actual inhalation exposure period. No contaminants were present in the feed or water at levels known to be capable of interfering with the results of this study.
- H. Environment: During the quarantine, exposure, and post-exposure observation periods, the rats were housed individually in stainless steel cages (18.4 x 16.5 x 15.9 cm). The cages were suspended over excrement pans (except during inhalation exposure). Deotized animal cage boards (Shepherd Specialty Papers, Kalamazoo, MI) were provided beneath the suspended cages. Animal room temperature and relative humidity (%RH) were maintained at 18 - 25°C and 28 - 63% RH. No excursions of animal room temperature or relative humidity occurred that were of a magnitude that would be expected to affect the results of this study. Fluorescent lighting was provided automatically on a 12 hours light: 12 hours dark schedule.
- I. Assignment to Groups: The rats were randomly assigned to groups of five male and five female rats by use of a computerized body-weight stratification procedure. Four groups of rats were exposed to atmospheres of the test substance. There was no control group.

- J. Clinical Observations: All rats were observed carefully for signs of toxicity immediately after removal from the exposure chamber and at least once per day during the 14-day observation period. To the maximum extent possible, animals were also observed during the exposures. During the two highest concentration exposures, most or all rats could not be adequately observed to allow any documentation of clinical signs. Even at lower concentrations, the animals that could be seen could not be thoroughly evaluated. Therefore, observations during exposures have not been included in the tabulated results.
- K. Body Weights: All test rats were weighed immediately before exposure, on post-exposure day 7 and just before necropsy.
- L. Necropsy: All test animals found dead were subjected to gross necropsy. At the end of the 14-day observation period, all surviving rats were euthanized following an intraperitoneal injection of sodium pentobarbital or CO₂ asphyxiation (by exsanguination) and subjected to gross necropsy.

The necropsy included examination of all body surfaces and openings and of the external surface of the brain, heart, lungs and respiratory tract, liver, spleen, kidneys, adrenals, gastrointestinal tract, gonads and urinary bladder. The gastrointestinal tract and urinary bladder were opened and examined if lesions were observed.

IV. RESULTS

- A. Exposure Concentrations: The exposure concentrations of N,N-Dimethyl-p-Toluidine in the test atmospheres are summarized in Table 1. The mean concentrations of N,N-Dimethyl-p-Toluidine as determined by chemical analysis of the filter collected (aerosol phase) and impinger collected (vapor phase) samples were 5.27 mg/l for the initial exposure and 1.73, 0.30 and 0.99 mg/l for the three subsequent exposures. Aerosol and vapor concentrations determined from individual samples are provided in Appendix A.
- B. Particle Size Distribution: The results of the particle size analysis are also shown in Table 1. Aerosol Mass Median Aerodynamic Diameter (MMAD) of the chamber atmosphere ranged from 0.23 to 0.57 μ m.
- C. Chamber Conditions: During exposures to 5.27, 1.73, 0.99 and 0.30 mg/l, the average chamber airflows were 132, 133, 124 and 141 l/min, respectively. The mean chamber temperature was 23°C (range 23 to 24°C), 23°C (range 23 to 24°C), 24°C (range 24 to 25°C), and 25°C (range 24 to 25°C) respectively, during the exposures to 5.27, 1.73, 0.99 and 0.30 mg/l. The mean relative humidity (%RH) was 22% (range 15%

to 30%), 23% (range 20% to 25%), 46% (range 45% to 48%) and 48% (range 45% to 51%), respectively, during these exposures. The percent O₂ in the chamber during all exposures was 21%.

- D. Mortality: The mortality for the four exposure groups is summarized in the following table:

Exposure ^a Conc., mg/l	Mortality (No. Dead/No. Tested)		
	Males	Females	Males & Females
5.27	5/5	5/5	10/10
1.73	3/5	5/5	8/10
0.30	0/5	0/5	0/10
0.99	0/5	0/5	0/10

^a Listed in order that exposures were conducted

Mortality data for individual rats is shown in Table 2. All rats exposed to 5.27 mg/l died during the exposure. Following exposure to 1.73 mg/l, four female rats died on the exposure day and the remaining female and three male rats died within two days post-exposure. Because of the generally all-or-none pattern of mortality, it was not possible to calculate a precise LC₅₀. However, the LC₅₀ can be estimated to be about 1.4 mg/l.

- E. Clinical Observations: The clinical observations are summarized in Table 3 and observations for individual animals are presented in Appendix B. Since many animals either could not be observed during exposure or could not be adequately observed, signs noted in some rats during exposures are not included in these tables. Clinical signs in rats exposed to 1.73 mg/l included hypoactivity, a comatose/prostrate condition, dyspnea or rapid respiration and salivation. Other incidental signs observed for some animals from this group included urine stains, eye discharge, ptosis, limb paralysis, nasal discharge, red material around the nose and red material around the eyes. The most frequently observed signs in rats exposed to 0.99 or 0.30 mg/l were nasal discharge and red material around the nose. Two male rats and one female rat from the 0.30 mg/l group were also reported to have dyspnea immediately after the exposure. Rats exposed to one of the two lower concentrations were free of signs by 1-2 days post-exposure.

- F. Body Weights: Body weights recorded prior to exposure and during the observation are tabulated and summarized in Table 4. For the 5.27, 1.73, 0.99 and 0.30 mg/l exposure groups, mean pre-exposure body weights ranged from 197 to 262 g for male rats and 160 to 192 g for female rats.

For male survivors of exposure to 1.73 mg/l and male and female survivors of exposure to 0.99 or 0.30 mg/l (all rats), weight gain was observed during both the first and second weeks of the observation period. Mean cumulative weight gain ranged from 73 to 91 g for male rats and 28 to 33 g for female rats.

- G. Gross Pathology: The gross necropsy observations are summarized in Table 5 and observations for individual animals are presented in Appendix C. No gross lesions were found in animals exposed to 0.99 or 0.30 mg/l. In rats exposed to the two higher concentrations, mottled lungs and red ovaries were frequently found and may have been exposure-related. Several rats from these groups also had gas-filled gastrointestinal organs. A few other lesions were observed in individual rats, but were not considered to be toxicologically significant.

V. CONCLUSION

A 4-hour exposure to an aerosol/vapor test atmosphere of N,N-Dimethyl-p-Toluidine at mean concentrations of 5.27 and 1.73 mg/l produced mortality indicating a steep dose-response relationship for acute inhalation exposure of Sprague-Dawley-derived rats. Although the precise LC_{50} could not be determined, it can be estimated to be about 1.4 mg/l. Exposure to 0.99 mg/l (990 mg/m³) is identified as a no-observable-effect level (NOEL).

VII. TABLES

TABLE 1

Summary of Exposure Concentrations and Particle Size Distribution

Exposure Conc. ^a , mg/l			Particle Size ^b					
			MMAD ^c , μm			GSD ^d		
<u>Mean^e</u>	<u>SD</u>	<u>%RSD</u>	<u>Mean^f</u>	<u>SD</u>	<u>%RSD</u>	<u>Mean^f</u>	<u>SD</u>	<u>%RSD</u>
5.27	1.38	26.19	0.23	0.12	52.17	5.65	1.83	32.39
1.73	0.05	2.89	0.26	0.01	3.85	3.09	0.57	18.45
0.30	0.05	16.67	0.57	0.16	28.07	6.10	2.04	33.44
0.99	0.14	14.14	0.53	0.04	7.55	3.45	0.95	27.54

^a Determined by chemical analysis

^b Determined with Quartz Crystal Microbalance Cascade Impactor, QCM

^c Mass Median Aerodynamic Diameter

^d Geometric Standard Deviation

^e Means of four determinations during a four-hour exposure period

^f Means based on 2 to 4 determinations during a four-hour exposure period

TABLE 2
Mortality
(5 Rats/Sex/Group)

<u>Exposure Conc., mg/l</u>	<u>Sex</u>	<u>Animal Number</u>	<u>Time of Death (Post-Exposure Day)</u>
5.27	M	01	0
		02	0
		03	0
		04	0
		05	0
	F	06	0
		07	0
		08	0
		09	0
		10	0
1.73	M	11	2
		12	2
		13	SAC
		14	SAC
		15	2
	F	16	0
		17	0
		18	0
		19	0
		20	1
0.30	M	21	SAC
		22	SAC
		23	SAC
		24	SAC
		25	SAC
	F	26	SAC
		27	SAC
		28	SAC
		29	SAC
		30	SAC
0.99	M	31	SAC
		32	SAC
		33	SAC
		34	SAC
		35	SAC
	F	36	SAC
		37	SAC
		38	SAC
		39	SAC
		40	SAC

SAC- Animal sacrificed at end of study

TABLE 3
 Summary of Clinical Observations
 (5 Rats/Sex/Group)

Clinical Observation	Exposure Conc., mg/l								
	5.27 ^a		1.73		0.30		0.99		
	M	F	M	F	M	F	M	F	
Urine stain	0	0	2	0	0	0	0	0	0
Eye discharge	0	0	3	1	0	1	0	2	
Ptosis	0	0	0	1	0	0	0	0	
Nasal discharge	0	0	1	0	5	5	3	2	
Salivation	0	0	3	1	0	1	0	0	
Dyspnea	0	0	1	5	2	1	0	1	
Rapid respiration	0	0	4	0	0	0	0	0	
Comatose	0	0	1	5	0	0	0	0	
Hypoactive	0	0	5	5	0	0	0	0	
Paralysis	0	0	1	0	0	0	0	0	
Prostrate	0	0	1	5	0	0	0	0	
Red material around nose	0	0	3	0	2	0	5	5	
Red material around eyes	0	0	2	0	0	0	0	0	

^a All 10 rats were found dead immediately following the exposure.

TABLE 4
Body Weights
(5 Rats/Sex/Group)

Exposure Conc., mg/l	Animal Number	Body Weight (g)			Cumulative Body Weight Change(g), Week 2-Initial	
		Initial	Post Exposure			
			Week 1	Week 2		
5.27	<u>MALES</u>					
		01	204	D		
		02	203	D		
		03	196	D		
		04	197	D		
		05	205	D		
		Mean	201			
		SD	4			
		<u>FEMALES</u>				
		06	147	D		
		07	174	D		
		08	160	D		
		09	155	D		
		10	166	D		
	Mean	160				
	SD	10				
1.73	<u>MALES</u>					
		11	206	D		
		12	221	D		
		13	220	249	322	102
		14	240	256	319	79
		15	222	D		
		Mean	222	253	321	91
		SD	12	5	2	16
		<u>FEMALES</u>				
		16	177	D		
		17	164	D		
		18	170	D		
		19	178	D		
		20	173	D		
	Mean	172				
	SD	6				

D = animal dead

TABLE 4

**Body Weights
(5 Rats/Sex/Group)
(Continued)**

Exposure Conc., mg/l	Animal Number	Body Weight (g)			Cumulative Body Weight Change(g), Week 2-Initial		
		Initial	Post Exposure				
			Week 1	Week 2			
0.30	<u>MALES</u>	21	268	304	349	81	
		22	291	338	386	95	
		23	244	267	300	56	
		24	260	286	324	64	
		25	248	277	316	68	
		Mean	262	294	335	73	
		SD	19	28	34	15	
		<u>FEMALES</u>	26	209	230	245	36
			27	192	198	228	36
			28	190	197	209	19
			29	195	203	206	11
			30	175	196	212	37
		Mean	192	205	220	28	
		SD	12	14	16	12	
0.99	<u>MALES</u>	31	197	240	298	101	
		32	190	226	282	92	
		33	204	239	304	100	
		34	215	256	297	82	
		35	181	215	261	80	
		Mean	197	235	288	91	
		SD	13	16	17	10	
		<u>FEMALES</u>	36	163	172	194	31
			37	153	171	189	36
			38	188	196	209	21
			39	154	164	183	29
			40	178	201	226	48
		Mean	167	181	200	33	
		SD	15	17	17	10	

D = animal dead

TABLE 5
 Summary of Gross Necropsy Observations
 (5 Rats/Sex/Group)

Exposure Conc., mg/l	Observation	Males	Females
5.27	Lungs, mottled, red	2	4
	Ovaries, dark red	0	3
	Small intestine, gas-filled	1	1
	Stomach, gas-filled	3	1
	Cecum, gas-filled	0	2
	Mandibular lymph node, red	1	0
1.73	Lungs, mottled, red	3	4
	Lungs, right anterior and right median lobes, mottled	0	1
	Liver, pale	1	0
	Stomach, gas-filled	2	2
	Gastrointestinal tract, gas-filled	1	0
	Small intestine, ileum, red	0	1
	Kidneys, pale	1	0
	Ovaries, red	0	3
	Mandibular lymph node, red	0	1
	Mediastinal lymph nodes, red	1	0
	Urinary bladder, distended with red fluid	1	0
	Urinary bladder, distended 15mm x 20mm	0	1
	0.30	None	5
0.99	None	5	5

VIII. APPENDICES

APPENDIX A

INDIVIDUAL EXPOSURE CONCENTRATION DETERMINATIONS

Date of Exposure	Sample Number	Aerosol Concentration ^a , mg/l		Vapor Concentration ^b , mg/l	Total Concentration ^c , mg/l
		Gravimetric	Chemical		
12-08-92	1	4.56	5.55	1.28	6.83
	2	3.14	3.00	1.47	4.47
	4 ^d	2.66	2.70	1.11	3.81
	5	4.45	4.58	1.39	5.97
	12-10-92	1	0.462	0.502	1.20
12-10-92	2	0.498	0.303	1.41	1.71
	3	0.500	0.487	1.21	1.70
	4	0.472	0.496	1.31	1.81
	12-16-92	1	0	0.036	0.32
12-16-92	2	0.016	0.033	0.27	0.30
	3	0.015	0.024	0.24	0.26
	4	0.030	0.021	0.25	0.27
	1-05-93	1	0.113	0.107	1.07
1-05-93	2	0.089	0.095	0.75	0.85
	3	0.096	0.093	0.89	0.98
	4	0.099	0.104	0.83	0.93

^a Determined by gravimetric and GC analysis of filter-collected samples

^b Determined by GC analysis of impinger-collected samples

^c Sum of aerosol concentration by chemical analysis and vapor concentration

^d Impinger samples not collected for sample no. 3, therefore filter sample results not reported

APPENDIX B

(Page 1 of 4)

CLINICAL OBSERVATIONS IN INDIVIDUAL RATS
(5.27 mg/l exposure concentration)

DAYS POST EXP	ANIMAL NUMBER									
	MALE RATS					FEMALE RATS				
	1	2	3	4	5	6	7	8	9	10
0	1	1	1	1	1	1	1	1	1	1
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										

- | | | | |
|----------------------------|----------------------|-----------------------|------------------------------|
| 0. No signs observed | 14. Cyanosis (skin) | 27. Reddened eye | 40. Diarrhea |
| 1. Animal found dead | 15. Jaundice (skin) | 28. Head tilt | 41. Ataxia |
| 2. Moribund | 16. Pale (skin) | 29. Malocclusion | 42. Comatose |
| 3. Abnormal posture | 17. Reddened (skin) | 30. Nasal discharge | 43. Convulsions |
| 4. Cold to touch | 18. Rough coat | 31. Salivation | 44. Hyperactive |
| 5. Emaciated | 19. Ulcer | 32. Dyspnea | 45. Hypoactive |
| 6. Hunched | 20. Urine stain | 33. Rales | 46. Irritable |
| 7. Missing anatomy | 21. Bulging eyes | 34. Rapid respiration | 47. Paralysis |
| 8. Prolapse | 22. Eye discharge | 35. Sneezing | 48. Prostrate |
| 9. Swelling | 23. Lacrimation | 36. Blood-urine | 49. Tremors |
| 10. Tissue Mass | 24. Micro-ophthalmia | 37. Colored urine | 50. Red material around eye |
| 11. Abscess | 25. Ocular opacity | 38. Blood-feces | 51. Red material around nose |
| 12. Alopecia | 26. Ptosis | 39. Colored feces | |
| 13. Compound stains (skin) | | | |

APPENDIX B
(Page 2 of 4)

CLINICAL OBSERVATIONS IN INDIVIDUAL RATS
(1.73 mg/l exposure concentration)

DAYS POST EXP	ANIMAL NUMBER									
	MALE RATS					FEMALE RATS				
	11	12	13	14	15	16	17	18	19	20
0	22,34,45,47,48	22,34,45,51	34,45,50	34,45	22,31,32,45	(1),32,42,45,48	(1),32,42,45,48	(1),32,42,45,48	(1),25,32,42,45,48	22,26,32,42,45,48
1	20,22,31,42,45,47,48,30	22,31,34,45,50,51	34,50	34,50	20,22,32,45,51					(1),22,31,32,42,45,48
2	1	1	0	0	(1),20,32,45,51					
3			0	0						
4			0	0						
5			0	0						
6			0	0						
7			0	0						
8			0	0						
9			0	0						
10			0	0						
11			0	0						
12			0	0						
13			0	0						
14			0	0						

- | | | | |
|----------------------------|----------------------|-----------------------|---|
| 0. No signs observed | 14. Cyanosis (skin) | 27. Reddened eye | 40. Diarrhea |
| 1. Animal found dead | 15. Jaundice (skin) | 28. Head tilt | 41. Ataxia |
| 2. Moribund | 16. Pale (skin) | 29. Malocclusion | 42. Comatose |
| 3. Abnormal posture | 17. Reddened (skin) | 30. Nasal discharge | 43. Convulsions |
| 4. Cold to touch | 18. Rough coat | 31. Salivation | 44. Hyperactive |
| 5. Emaciated | 19. Ulcer | 32. Dyspnea | 45. Hypoactive |
| 6. Hunched | 20. Urine stain | 33. Rales | 46. Irritable |
| 7. Missing anatomy | 21. Bulging eyes | 34. Rapid respiration | 47. Paralysis |
| 8. Prolapse | 22. Eye discharge | 35. Sneezing | 48. Prostrate |
| 9. Swelling | 23. Lacrimation | 36. Blood-urine | 49. Tremors |
| 10. Tissue Mass | 24. Micro-ophthalmia | 37. Colored urine | 50. Red material around nose |
| 11. Abscess | 25. Ocular opacity | 38. Blood-feces | 51. Red material around eyes |
| 12. Alopecia | 26. Ptosis | 39. Colored feces | (1). Animal found dead after observations |
| 13. Compound stains (skin) | | | |

APPENDIX B
(Page 3 of 4)

CLINICAL OBSERVATIONS IN INDIVIDUAL RATS
(0.30 mg/l exposure concentration)

DAYS POST EXP	ANIMAL NUMBER									
	MALE RATS					FEMALE RATS				
	21	22	23	24	25	26	27	28	29	30
0	30,32	30,32,50	30	30	30,50	30,32	30	30	22,30	30,31
1	30	0	30	0	0	0	30	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0

- | | | | |
|----------------------|----------------------|-----------------------|------------------------------|
| 0. No signs observed | 14. Cyanosis (skin) | 27. Reddened eye | 40. Diarrhea |
| 1. Animal found dead | 15. Jaundice (skin) | 28. Head tilt | 41. Ataxia |
| 2. Moribund | 16. Pale (skin) | 29. Malocclusion | 42. Comatose |
| 3. Abnormal posture | 17. Reddened (skin) | 30. Nasal discharge | 43. Convulsions |
| 4. Cold to touch | 18. Rough coat | 31. Salivation | 44. Hyperactive |
| 5. Emaciated | 19. Ulcer | 32. Dyspnea | 45. Hypoactive |
| 6. Hunched | 20. Urine stain | 33. Rales | 46. Irritable |
| 7. Missing anatomy | 21. Bulging eyes | 34. Rapid respiration | 47. Paralysis |
| 8. Prolapse | 22. Eye discharge | 35. Sneezing | 48. Prostrate |
| 9. Swelling | 23. Lacrimation | 36. Blood-urine | 49. Tremors |
| 10. Tissue Mass | 24. Micro-ophthalmia | 37. Colored urine | 50. Red material around nose |
| 11. Abscess | 25. Ocular opacity | 38. Blood-feces | |
| 12. Alopecia | 26. Ptosis | 39. Colored feces | |

APPENDIX B
(Page 4 of 4)

CLINICAL OBSERVATIONS IN INDIVIDUAL RATS
(0.99 mg/l exposure concentration)

DAYS POST EXP	ANIMAL NUMBER									
	MALE RATS					FEMALE RATS				
	31	32	33	34	35	36	37	38	39	40
0	30.50	50	30.50	30.50	50	22.50	50	22.50	30.32.50	30.50
1	0	0	50	0	0	0	0	0	50	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0

- | | | | |
|----------------------------|----------------------|-----------------------|------------------------------|
| 0. No signs observed | 14. Cyanosis (skin) | 27. Reddened eye | 40. Diarrhea |
| 1. Animal found dead | 15. Jaundice (skin) | 28. Head tilt | 41. Ataxia |
| 2. Moribund | 16. Pale (skin) | 29. Malocclusion | 42. Comatose |
| 3. Abnormal posture | 17. Reddened (skin) | 30. Nasal discharge | 43. Convulsions |
| 4. Cold to touch | 18. Rough coat | 31. Salivation | 44. Hyperactive |
| 5. Emaciated | 19. Ulcer | 32. Dyspnea | 45. Hypoactive |
| 6. Hunched | 20. Urine stain | 33. Rales | 46. Irritable |
| 7. Missing anatomy | 21. Bulging eyes | 34. Rapid respiration | 47. Paralysis |
| 8. Prolapse | 22. Eye discharge | 35. Sneezing | 48. Prostrate |
| 9. Swelling | 23. Lacrimation | 36. Blood-urine | 49. Tremors |
| 10. Tissue Mass | 24. Micro-ophthalmia | 37. Colored urine | 50. Red material around nose |
| 11. Abscess | 25. Ocular opacity | 38. Blood-feces | |
| 12. Alopecia | 26. Ptosis | 39. Colored feces | |
| 13. Compound stains (skin) | | | |

APPENDIX C
(Page 1 of 3)

GROSS NECROPSY OBSERVATIONS IN INDIVIDUAL RATS
(5.27 mg/l exposure concentration)

Animal Number	Sex	GROSS NECROPSY OBSERVATIONS
01	M	None
02	M	Lungs, mottled, red; small intestine, gas-filled; stomach, gas-filled; mandibular lymph node, red
03	M	Lungs, mottled, red
04	M	Stomach, gas-filled
05	M	Stomach, gas-filled
06	F	Lungs, mottled, red; ovaries, red
07	F	Lungs, mottled, red; small intestine, gas-filled; cecum, gas-filled
08	F	Lungs, mottled, red; ovaries, red
09	F	Ovaries, dark red; stomach, gas-filled; thoracic cavity, dark red fluid
10	F	Lungs, mottled, red; cecum, gas-filled

APPENDIX C
(Page 2 of 3)

GROSS NECROPSY OBSERVATIONS IN INDIVIDUAL RATS
(1.73 mg/l exposure concentration)

Animal Number	Sex	GROSS NECROPSY OBSERVATIONS
11	M	Lungs, mottled, red; stomach, gas-filled; liver, pale; kidneys, pale; urinary bladder, distended with red fluid
12	M	Lungs, mottled, red; gastrointestinal tract, gas-filled; mediastinal lymph nodes, dark red
13	M	None
14	M	None
15	M	Lungs, mottled, red; stomach, gas-filled
16	F	Lungs, right anterior and right median lobes, mottled; stomach, gas-filled; ovaries, red
17	F	Lungs, mottled, red; ovaries, red; stomach, gas-filled
18	F	Lungs, mottled, red
19	F	Lungs, mottled, red; ovaries, red; small intestine ileum, appears red
20	F	Lungs, mottled, red; mandibular lymph node, red; urinary bladder, distended, 15mm x 20mm

APPENDIX C
(Page 3 of 3)

GROSS NECROPSY OBSERVATIONS IN INDIVIDUAL RATS
(0.30 mg/l exposure concentration)

Animal Number	Sex	GROSS NECROPSY OBSERVATIONS
21	M	None
22	M	None
23	M	None
24	M	None
25	M	None
26	F	None
27	F	None
28	F	None
29	F	None
30	F	None

GROSS NECROPSY OBSERVATIONS IN INDIVIDUAL RATS
(0.99 mg/l exposure concentration)

Animal Number	Sex	GROSS NECROPSY OBSERVATIONS
31	M	None
32	M	None
33	M	None
34	M	None
35	M	None
36	F	None
37	F	None
38	F	None
39	F	None
40	F	None

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From: Ellen R. Stephens

ChemFirst Inc.

Phone: 601-938-2219

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REMARKS: Urgent For your review Reply ASAP Please comment

Per our conversation, a copy of the MSDS for DMPT is attached. None of the information on the MSDS is considered confidential.

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FIRST CHEMICAL CORPORATION

POST OFFICE BOX 7005 • PASCAGOULA, MISSISSIPPI 39558
TELEPHONE (601) 762-0870 TWX 510-990-3361

Name: **FIRSTCURE® DMPT**

Rev. A -- Date Prepared: January 22, 1997

MATERIAL SAFETY DATA SHEET

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Product Identifier: FIRSTCURE® DMPT
General Use: Amine Liquid Cure Accelerator
Product Description: N,N-Dimethyl-p-Toluidine (DMPT)
Formula: C₉H₁₃N
Molecular Weight: 135

MANUFACTURER:

First Chemical Corporation
1001 Industrial Road
Pascagoula, MS 39581
(601) 762-0870

EMERGENCY TELEPHONE NUMBERS:

CHEMTREC (800) 424-9300
24 Hours Everyday

2. COMPOSITION / INFORMATION ON INGREDIENTS

	<u>wt. %</u>	<u>CAS Registry #</u>
N,N-Dimethyl-p-Toluidine	99.0	99-97-8

	EXPOSURE LIMITS 8 hrs. TWA (ppm)	
	<u>OSHA PEL</u>	<u>ACGIH TLV</u>
N,N-Dimethyl-p-Toluidine	None	None

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW:

Clear colorless liquid, but darkens with exposure to light and air. Sweet aromatic amine odor.

Harmful if inhaled.

May cause skin irritation.

May cause allergic skin reaction.

Overexposure may cause cyanosis.

POTENTIAL HEALTH EFFECTS:

INHALATION:

Based on animal studies, this material may cause elevated methemoglobin in the blood. Symptoms include headaches, weakness and dizziness, and can be recognized by blue color of the lips, fingernails, nose, ear lobes and other extremities. High level exposures can cause shallow breathing, confusion, rapid heart beat, unconsciousness and death. Vapor or mist is irritating to mucous membranes and the upper respiratory tract.

Name: FIRSTCURE® DMPT

Rev. A - Date Prepared: January 22, 1997

EYE CONTACT:

May cause eye irritation.

SKIN CONTACT:

May cause skin irritation. FIRSTCURE® DMPT can be absorbed through the intact skin causing systemic toxicity. Prolonged or repeated exposure may cause allergic skin reaction in some people. Additional symptoms are similar to those caused by inhalation.

INGESTION:

May cause methemoglobinemia.

TARGET ORGANS:

Liver, central nervous system, blood, and skin.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE:

Overexposure may aggravate existing cardiovascular or respiratory conditions, blood disorders, or dermatitis.

CARCINOGENICITY:

None of the components in this product at concentrations equal to or greater than 0.1% is listed by IARC, NTP, OSHA, or ACGIH as a carcinogen.

4. FIRST AID MEASURES

INHALATION:

Remove to fresh air immediately. If not breathing give artificial respiration. If breathing is difficult, give oxygen. Consult a physician.

EYE CONTACT:

Flush eyes with water for at least 15 minutes. Have eyes examined and treated by a physician.

SKIN CONTACT:

Speed is essential in removing FIRSTCURE® DMPT from skin, hair, and nails. Immediately flush skin with water for at least 15 minutes while removing contaminated clothing and shoes. Wash skin, hair, and nails with soap and water. Have the person lie down and keep warm and quiet. Call a physician. If breathing is difficult, give oxygen.

INGESTION:

Immediately induce vomiting as directed by a physician. Repeat until vomit is clear. Never give anything by mouth to an unconscious person. Consult a physician.

NOTE TO PHYSICIAN:

Absorption of this product into the body leads to the formation of methemoglobin, which in sufficient concentration causes cyanosis. Because reversion of methemoglobin to hemoglobin occurs spontaneously after termination of exposure, moderate degrees of cyanosis need be treated only by supportive measures such as bed rest and oxygen inhalation. Thorough cleansing of the entire contaminated area of the body is of utmost importance. If cyanosis is severe, intravenous injection of methylene blue, 1-2 mg/kg body weight over a 5 minute period as a 1 percent solution may be of value. If elevated methemoglobin persists after an hour, the treatment may be repeated, but the total dose should not exceed 7 mg/kg body weight. Cyanocobalamin (Vitamin B-12), 1 mg intramuscularly is reported to speed recovery. Intravenous fluids and blood transfusions may be indicated in very severe exposures.

5. FIRE FIGHTING MEASURES

Flashpoint:	181°F (83°C)
Method:	Tag Closed Cup (TCC)
Flammable Limits in Air, % by volume:	Lower: Not available Upper: Not available
Autoignition Temperature:	Not available
Extinguishing Media:	Water spray, fog, foam, carbon dioxide, dry chemical

UNUSUAL FIRE AND EXPLOSION HAZARDS:

Vapors may flow along surfaces to distant ignition sources and flash back. Toxic vapors may be given off at high temperatures.

FIRE FIGHTING INSTRUCTIONS:

Use water spray to cool containers and fire exposed surfaces. Shut off fuel to fire if possible to do so without hazard.

FIRE FIGHTING EQUIPMENT:

Wear full protective clothing with self-contained positive pressure breathing apparatus. If there is potential for skin exposure to FIRSTCURE® DMPT, see Section 8 of this MSDS.

HAZARDOUS COMBUSTION PRODUCTS:

Carbon monoxide, Nitrogen oxides.

6. ACCIDENTAL RELEASE MEASURES

SPILL OR LEAK PROCEDURES:

Evacuate area and keep personnel upwind. Cut off any source of ignition and ventilate spill area. Contain spill with absorbent material. Transfer absorbent and other contaminated materials to a UN approved covered container for disposal. Consult with Federal, State, and local regulatory agencies to determine acceptable clean-up levels. Comply with Federal, State, and local regulations on reporting releases.

7. HANDLING AND STORAGE:

STORAGE TEMPERATURE:

Storage in a cool, dry, well-ventilated area at 40° - 90°F (5° - 32°C) is recommended.

GENERAL:

Keep in original tightly closed containers.
Keep away from strong oxidizing agents or acids.
Prevent skin and eye contact.
Avoid breathing vapors.
Thorough showering at the end of the work shift is strongly recommended.
Work clothes should be laundered daily.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

PERSONAL PROTECTION:

RESPIRATORY PROTECTION:

If vapors of FIRSTCURE® DMPT are present, use, as a minimum, a NIOSH approved full-face respirator with canisters or cartridges specifically approved for use with organic vapors. Whenever cartridge or canister respirators are used, insure the frequent changing of the filter element. Use a supplied air respirator when in doubt of the atmospheric concentration. Consult 29 CFR 1910.134 regarding use of respirators.

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PROTECTIVE CLOTHING:

Take all precautions to prevent skin contact. Use supported neoprene gloves for routine work and butyl rubber gloves when there is a probability of liquid contact. Do not use nitrile rubber as a protective material. Additional protection, such as a butyl rubber full body suit may be required depending upon conditions.

EYE / FACE PROTECTION:

Use chemical goggles. Wear a full face shield if splashing is possible.

9. PHYSICAL AND CHEMICAL PROPERTIES

Vapor Pressure: 5.0 mmHg at 162°F (72°C)
Specific Gravity: 0.930
Solubility In Water: Negligible (<0.1%)
Boiling Point: 412°F (211°C)
Physical State: Liquid

Vapor Density: 4.6 (Air = 1)
Evaporation Rate: 0.5 (Butyl Acetate = 1)
pH: Not applicable
Odor: Disagreeable amine
Appearance: Clear colorless liquid, but darkens with exposure to light and air

10. STABILITY AND REACTIVITY

GENERAL:

Stable at normal temperatures and conditions of storage.

INCOMPATIBLE MATERIALS AND CONDITIONS TO AVOID:

Reacts violently with strong oxidizers, strong acids, and hypochlorite bleaches. FIRSTCURE® DMPT will attack some forms of plastics, rubber, and coatings.

HAZARDOUS DECOMPOSITION:

Carbon monoxide, Nitrogen oxides.

HAZARDOUS POLYMERIZATION:

Will not normally occur.

11. TOXICOLOGICAL INFORMATION

DATA FOR FIRSTCURE® DMPT:

INHALATION:	LC ₅₀ , rat (4 hr): 254 ppm, moderately toxic.
EYE CONTACT:	FHSA score 6.4/110, slightly irritating.
SKIN CONTACT:	LD ₅₀ , rat: >2000 mg/kg, no more than slightly toxic. Primary Irritation Index: 3.6/8.0, moderately irritating. Both positive and negative results found for sensitization in guinea pigs; reported to cause sensitization in humans.
INGESTION:	LD ₅₀ , rat: 1650 mg/kg, slightly toxic. Methemoglobinemia noted after single oral doses.
GENOTOXICITY:	Not mutagenic in bacterial cells in culture; caused chromosome damage in animal cells in culture.
TARGET ORGANS:	Liver, central nervous system, blood, and skin.

12. ECOLOGICAL INFORMATION.

No information is available for FIRSTCURE® DMPT.

13. DISPOSAL CONSIDERATIONS

DISPOSAL METHODS:

Consult 40 CFR, Parts 261 and 268, State, and local regulations for guidance on disposal of this product. Incineration at a facility with proper Federal and State issued permits is the recommended method for disposal

CONTAINER DISPOSAL:

Empty containers retain product residue. Observe all hazard precautions. Keep away from heat, sparks, and flames. Do not distribute, make available, or reuse empty containers except for storage and shipment of original product. Remove all hazardous product residue, and puncture or otherwise destroy empty containers before disposal. Consult 40 CFR 261 and 268 for guidance on disposal.

Name: FIRSTCURE® DMPT

Rev. A - Date Prepared: January 22, 1997

14. TRANSPORT INFORMATION**DOT/IMO/ICAO/IATA:**

Proper Shipping Name: TOXIC LIQUIDS, ORGANIC, N.O.S.
(N,N-DIMETHYL-p-TOLUIDINE)
Hazard Class: 6.1
Identification Number: UN 2810
Packing Group: III
Labels Required: Toxic
IMDG Page No.: 6270-1

15. REGULATORY INFORMATION**TSCA (Toxic Substance Control Act):**

This product is listed on the TSCA Inventory.

SARA TITLE III (Superfund Amendments and Reauthorization Act):

311/312 Hazard Categories.

Acute.

313 This product is not subject to the reporting requirements of Section 313 of the Emergency Planning and Community Right-To-Know Act of 1986 and of 40 CFR 372.

CERCLA (Comprehensive Response Compensation and Liability Act):

Not Reportable.

We recommend you contact local authorities to determine if there may be other local reporting requirements.

16. OTHER INFORMATION

Preplacement and periodic physical examinations should be performed on all individuals working in FIRSTCURE® DMPT exposure areas. Individuals with liver or kidney disorders, impaired cardiovascular status, or a history of alcoholism should avoid exposure. Because the long term human health effects from exposure to FIRSTCURE® DMPT have not been fully evaluated, exposure should be kept to the lowest level possible. This material is for industrial use. Use only under the supervision of a technically qualified individual.

Name: FIRSTCURE® DMPT

Rev. A -- Date Prepared: January 22, 1997

Label Information:

HMIS Codes

Health - 2

Fire - 2

Reactivity - 0

Specific Hazard - None

REVISION SUMMARY:

Rev. A -- Initial 16 Section MSDS.

Prepared by: Steven C. Dawson, CIH
Manager, Industrial Hygiene & Health

The information included in this document is taken from sources, or based on data believed to be reliable and given in good faith. No warranty is made, however, as to the absolute correctness of any of this information, or that additional or other measures may not be required under particular conditions. The data in this Material Safety Data Sheet relates only to the specific material designated and does not relate to use in combination with any other material or in any process. Please refer to the OSHA Hazard Communication Standard 29 CFR 1910.1200 for guidance in the use of this information.