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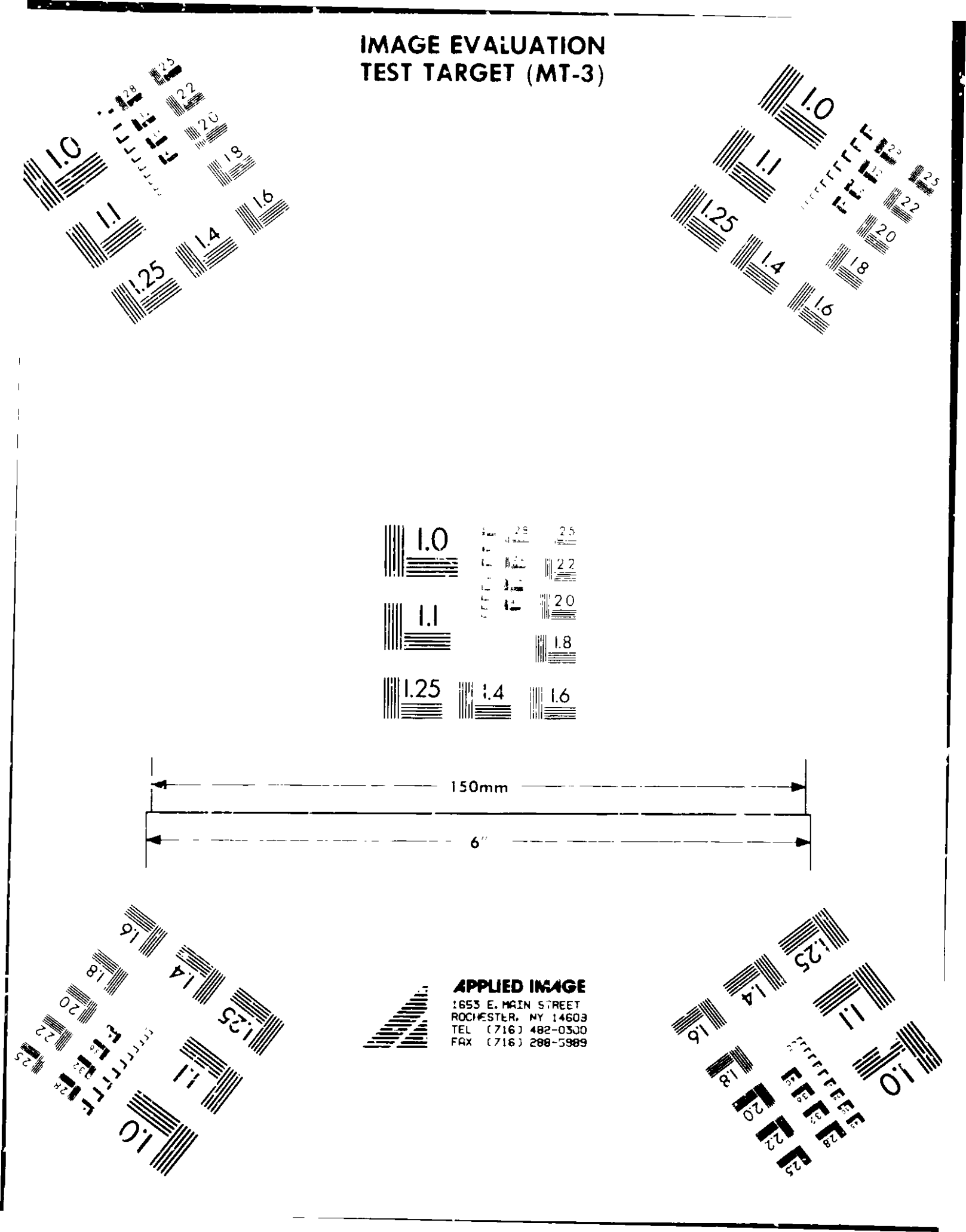
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ORAL TOXICITY STUDY OF COMPOUNDS, INCLUDING P-NITRODICHLOROBENZENE, IN [] BUILDING WITH COVER LETTER DATED 05/10/94 (SANITIZED)

Chemical Category
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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,

K.D.Dastur

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

/pmt
Enclosure

8694000076 1

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.	Dimethy Sulfate Permeation Testing	HLR# 538-81
9	Teratogenicity Study of Dimethyl Sulfate in Rats	HLR# 535-81
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 Aosorption 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

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MR-187
Report # 13-19

cc: [redacted] CSM

" [redacted]

[redacted] TSM

May 9, 194[redacted]

[redacted]

TOXICITY OF COMPOUNDS USED IN [redacted] BUILDING

Preliminary oral toxicity studies have been carried out under Medical Research Project [redacted] on a series of compounds used in the [redacted] Building No. 750. The eleven compounds tested were Orthoanisidine, n-Butyl-p-aminophenol, 2-Chlor-amino-toluene, p-Toluidine, p-Nitroaniline, p-Nitrodichlorobenzene, p-Nitrophenetole, Alpha naphthol, Naphthionic acid, Piperidine, and Diagen A.

Acute oral toxicity was tested by determining the approximate lethal dose (ALD) for rats. The method of Deichmann and LeBlanc* was used wherein single doses of increasing amounts were given to a series of rats by stomach tube. The minimum dose which killed was considered the ALD.

Chronic or cumulative toxicity was tested by administering orally to 5 rats approximately 1/5 the ALD five times a week for 2 weeks so that a total of twice the lethal dose was administered. The rats were checked for change in weight and any unusual clinical symptoms. Following the final treatment they were observed for a period of from one to two weeks prior to being sacrificed. Tissues of all rats were examined for gross and micropathology.

The details of the tests performed for each compound were as follows:

o-Anisidine

Acute Oral Toxicity: The ALD for rats was found to be 1500 mg/kg. The material was administered by stomach tube as a 50% solution in peanut oil. The rat receiving the 1500 mg/kg dose died within 48 hours after treatment. The lungs were found to be congested and [redacted] atelectatic.

*W. Deichmann and T. J. LeBlanc, J. Ind. Hyg. & Tox., 25, 415, 1943.

Chronic Oral Toxicity: Ten doses of 300 mg/kg as a 10% solution in peanut oil were administered to 6 rats over a period of two weeks. The rats showed an initial loss of weight but a subsequent normal gain. When sacrificed, no pathology was found which could be attributed to o-anisidine.

Conclusions: From the standpoint of oral toxicity, o-anisidine is not a very toxic compound. 1500 mg/kg were required to produce death in the rat. In addition, cumulative toxicity did not occur under the conditions described.

n-Butyl-p-aminophenol

Acute Oral Toxicity: The ALD was found to be 450 mg/kg. The compound was administered as a 40% solution in peanut oil heated to 50° C. The animals died within 21 hours. The only pathology noted was the presence of albumin in the kidneys.

Chronic Oral Toxicity: Ten treatments of 90 mg/kg each as a 5% solution in peanut oil containing 10% acetone were given. The rats were uncomfortable following the treatments. They also showed a definite slowing of the rate of gain in weight until a week after the final treatment, although they did not go below the original weight at any time. They were killed two weeks after the final treatment and no pathology attributable to the material was detected.

Conclusions: n-Butyl-p-aminophenol is a moderately toxic compound when absorbed through the gastro-intestinal tract. There was no evidence of cumulative toxicity under the conditions of our experiment.

Information on the toxicity of this compound in particular has not been reported but the aminophenols in general are known to cause skin sensitization among workers in the dye and photographic industries and to cause the formation of methemoglobin.

2-Chlor-4-Aminotoluene

Acute Oral Toxicity: The material was given as a 50% solution in peanut oil. 1500 mg/kg was found to be the ALD. Pain and weakness occurred 10 minutes after the dose was given and was followed by unconsciousness and

death within 22 hours. Both rats showed slight congestion of the lungs, and one had evidence of gastritis, but the cause of death was not apparent.

Chronic Oral Toxicity: 300 mg/kg as a 10% solution in peanut oil was fed ten times to each of 6 rats. After the third and fourth treatments the rats were ill and cyanotic. The reactions continued after the subsequent treatments but the intensity slackened and by the tenth they showed some improvement. They were killed 11 days after the final dose. Gross and micropathological examination revealed no pathology which could be attributed to 2-Chlor-4-aminotoluene, but foci of blood formation were consistently found in the spleen.

Conclusions: 2-Chlor-4-aminotoluene is not highly toxic as far as single oral doses are concerned. Since other chloranilidines have been shown to cause cyanosis and depression, presumably through formation of methemoglobin, it is probable that the same mechanism is involved with 2-Chlor-4-aminotoluene. This would be consistent with the observations on the chronic treatments in which the decrease in cyanosis during the latter part of the treatment period was probably due to compensatory activity of the hemopoietic system, since foci of blood formation were found in the spleens of the rats.

p-Toluidine

Acute Oral Toxicity: The material was administered as a 50% solution in peanut oil containing 15% acetone. The LD_{50} was 1000 mg/kg. The material caused pain, weakness, cyanosis, and death within 44 hours. Pathological examination indicated damage to the liver and kidneys.

Chronic Oral Toxicity: Ten doses of 200 mg/kg each were given as a 6% solution in peanut oil containing 15% acetone. The rats became pale and weak after six treatments but regained normal strength and color a week after treatment ended. The rats showed a marked loss of weight until the fifth treatment followed by a slow gain until the last week of observation when they began to gain rapidly. They were sacrificed 12 days after the final treatment and showed evidence of damage to the spleen, kidneys and liver.

Conclusions: p-Toluidine is only moderately toxic by single acute oral dose. Its action is apparently similar to that of aniline, causing anemia and formation of methemoglobin. Cases of industrial poisoning from toluidine have been reported and acute cases are usually characterized by

cyanosis and mental confusion which may be due to cerebral anoxia. Injury to the kidneys has been reported in workers, and was also observed in our rats.

p-Nitroaniline

Acute Oral Toxicity: The ALD was determined by administering the compound as a 40% solution in peanut oil and it was found to be 3375 mg/kg. Even sublethal doses caused weakening and cyanosis, while lethal doses produced tremors in addition. The urine contained a bright yellow pigment. Microscopic examination indicated damage to the liver, and the kidneys were distended with albuminous fluid.

Chronic Oral Toxicity: p-Nitroaniline in 10 doses of 675 mg/kg each, was administered to rats as a 20% solution in peanut oil. One rat died after the second treatment and one after the sixth. The other four survived the ten doses and were sacrificed after a ten-day observation period. The rats were in pain after each treatment. Their eyes and skin appeared yellow as did the urine, and there was generalized weakness. The average weight of the four survivors showed a sharp drop until the eighth treatment which was followed by a slow rise until the last week of observation which was marked by a rapid gain in weight. The original weight, however, was never again attained.

On microscopic examination the kidneys were observed to have granulation of the tubular epithelium and occasional vacuolation.

Conclusion: The acute oral toxicity of p-Nitroaniline is fairly low, but the results do show a tendency toward cumulative effects, and p-Nitroaniline has frequently been implicated in human cases of poisoning. Lewin (Gifte u. Vergiftungen, 1929) states that 40 mg/kg of p-Nitroaniline by intravenous injection kills animals, and he reports a fatal case of human p-Nitroaniline poisoning of industrial origin. The Encyclopedia of Occupation and Health (International Labor Office) states that the fatal dose for dogs of o-Nitroaniline is 500 mg/kg, and "is certainly smaller for p-Nitroaniline". The route of administration was not described. It is further stated that p-Nitroaniline in practice causes the greatest number of poisoning cases, of dermatitis, and of conjunctivitis.

Lobo-Mondonca, (Indian Med. Gaz. LL, 673) has reported cases of poisoning in textile workers. The dye was absorbed through the skin and caused paralysis of the central nervous system, marked cyanosis and sometimes death. Methemoglobin was found in the blood and hemoglobin and hematoporphyrin were found in the urine.

These results suggest that some species, including human beings, may be relatively more susceptible to p-Nitroaniline than the rat.

p-Nitrochlorobenzene

Acute Oral Toxicity: The material was administered as a 20% solution in peanut oil warmed to 50° C. The ALD was 670 mg/kg. All treated rats became cyanotic. In rats treated with sublethal doses it lasted 24 hours after treatment. The rat receiving 670 mg/kg lived nearly 48 hours after dosing. Pathological examination revealed necrosis and hemorrhage of the liver and incipient necrosis of the convoluted tubules of the kidney. The bladder contained blood tinged urine.

Chronic Oral Toxicity: Ten chronic doses of 135 mg/kg each as a 5% solution in peanut oil were administered to each of six rats. One rat died after the fourth exposure and one after the eighth. Both these rats were found to have acute necrosis around the hepatic veins of the liver and the presence of albumin and casts in the kidney tubules and granular epithelium in the case of one rat. The remaining four rats survived 10 treatments and were sacrificed twelve days after the final treatment. The rats were cyanotic during the early part of the treatment period and showed a rapid loss in weight throughout treatment and a subsequent gain during the observation period. However they barely exceeded their initial weight. The spleens of these animals were large and congested and showed signs of increased blood formation. This increased activity was probably due to the presence of methemoglobin. The nuclei of the liver cells showed slight variation in staining quality and the kidneys evidence of damage.

Conclusions: As in aniline poisoning the nitro benzene compounds produce breakdown products which cause the formation of methemoglobin with subsequent hemolysis and anemia. As far as acute toxicity is concerned p-Nitrochlorobenzene is moderately toxic with an ALD for rats at 670 mg/kg. Regeneration of blood after acute poisoning is fairly rapid.

Chronic exposure to the compound caused similar blood changes and was fatal in the case of two rats. Blood regeneration is slow in chronic exposure and apparently varies greatly with the individual.

p-Nitrophenetole

Acute Oral Toxicity: p-Nitrophenetole was administered as a 25% solution in peanut oil containing 15% acetone and the ALD was found to be 7500 mg/kg. Doses up to 4000 mg/kg produced no symptoms whatsoever. The rat receiving 5000 mg/kg, however, suffered from pain, weakness, and bronchial irritation, for 24 hours after treatment. At the 7500 mg/kg level the rat immediately became ill, unconscious and died within 24 hours. Autopsy disclosed congestion and edema of the lungs.

Chronic Oral Toxicity: Ten doses of 1500 mg/kg each, as a 25% solution in peanut oil-acetone were administered to six rats. They exhibited a slowing in the rate of gain of weight up to the seventh treatment after which there was a normal gain. At no time, however, did they fall below their pre-exposure weight. Three of the rats voided bright yellow urine throughout the treatment period. The animals were killed twelve days after treatment and no pathology was detected.

Conclusions: p-Nitrophenetole is a relatively non-toxic compound, nor did a cumulative toxicity show up under the conditions of our test.

Alpha Naphthol

Acute Oral Toxicity: The ALD was found to be 1000 mg/kg. The material was administered as a 50% solution in peanut oil. Rats receiving lethal doses suffered from diarrhea and died within 18 hours after treatment. Pathological examination indicated congestion and edema of the lungs, albumin in the kidney tubules and superficial necrosis of the stomach.

Chronic Oral Toxicity: Alpha naphthol as a 10% solution in peanut oil was fed ten times in doses of 800 mg/kg. The rats were pale during the treatment period and voided an abnormally large amount of urine. They showed a marked drop in weight throughout treatment but a normal gain during the observation period. Pathological examination indicated no pertinent pathology.

Conclusions: Alpha naphthol was not found to be a highly toxic compound although it is said to be more toxic than Beta naphthol.

The frequency of urination in the rats on chronic exposure was probably due to the known irritating effect of Alpha naphthol on the kidneys. The intensity and duration of our chronic exposure, however, did not produce changes of organic kidney damage that could be detected grossly or microscopically when the rats were sacrificed 10 days after the last treatment.

Naphthionic Acid

Acute Oral Toxicity: Doses up to 7500 mg/kg as a 50% solution in peanut oil were given to rats. The animals showed no ill effects and all survived. They were sacrificed and gross and microscopic examination of the tissues did not reveal any pathology.

Chronic Oral Toxicity: 2500 mg/kg was fed 10 times to each of 6 rats. They were somewhat uncomfortable after treatment and drank much water. They lost weight until the fifth treatment, gained slowly until the tenth, and gained rapidly during the observation period which lasted 10 days before the rats were sacrificed. No pathology which could be attributed to the compound was detected.

Conclusions: Naphthionic acid is relatively non-toxic when taken under the conditions described.

Piperidine

Acute Oral Toxicity: The ALD was determined to be 450 mg/kg when administered to rats as a 50% solution in water. The rats exhibited marked weakness and lethargy and died in from one to ninety hours depending on the size of the dose. Postmortem examination revealed edema of the lungs and necrosis of the stomach.

Chronic Oral Toxicity: 90 mg/kg as a 5% solution in water was given to rats ten times over a two week period. There was a marked loss in weight until the third treatment, followed by a rise to the original weight by the ninth day after the final treatment. Pathological examination indicated necrosis of the liver and possible kidney changes. The remainder of the rats were killed ten days after the final treatment. Four of the five showed possible kidney damage or the presence of hyaline casts.

Conclusions: Piperidine is said to be similar to nicotine which is known to cause pronounced paralysis of the central nervous system and of skeletal muscle motor endings. It is a moderately toxic compound with its ALD at 450 mg/kg and in this dosage takes a relatively long time to kill.

Chronic exposure to piperidine caused a temporary loss in weight and was the probable cause of death of [illegible]. Kidney damage though slight appeared in [illegible] rats indicating that cumulative toxicity may exist.

Diagen A

Acute Oral Toxicity: Diagen A was administered to rats by stomach tube in its original form. 7500 mg/kg the maximum feasible dose did not kill. The rat receiving this dose, however, when sacrificed 10 days after treatment showed evidence of chronic gastritis localized at junction of squamous and glandular portions.

Chronic Oral Toxicity: Ten doses of 1100 mg/kg each were givento each of 6 rats over a period of two weeks. There was an initial loss of weight but it was followed by a rapid gain. The animals were sacrificed eleven days after the final treatment and no pathology attributable to Diagen A could be detected.

Conclusions: From the standpoint of oral intake Diagen A is relatively non-toxic. Diagen Bordeau which was tested by this laboratory was also found to be equally non-toxic by mouth, but was found to be a mild skin irritant.

General Summary:

The results of our tests are summarized in the following table, in which the compounds are arranged in order of decreasing acute toxicity.

Compound	ALD	Cumulative Effects
Piperidine	450 mg/kg	Yes
n-Butyl-p-aminophenol	450	None observed
p-Nitro-dichlorobenzene	670	Yes
Alpha naphthol	1000	Yes
p-Toluidine	1000	Yes
o-Anisidine	1500	None observed
2-[illegible]-aminotoluene	1500	Yes
p-Nitroaniline	3375	Yes
[illegible]phenetole	7500	None observed
[illegible]	7500	[illegible]
[illegible] Acid	7500	[illegible]

While none of these materials is highly toxic [illegible] they are probably toxic enough to cause industrial poisoning in [illegible] since most of the compounds tested [illegible] compounds of [illegible] injurious to the kidneys.

The compounds discussed reach the human organism by skin absorption, by inhalation and by oral ingestion. The first two are the more important industrially. The tests performed give the approximate lethal dose and some idea of the danger of cumulative toxicity. They do not exclude the possibility of pathology occurring when exposure covers very long periods of time.

HASKELL LABORATORY OF
INDUSTRIAL TOXICOLOGY

John H. Boulger, M. D.
Director

BY: John A. Zapp, Jr., Ph.D.
Assistant Director

JAZ:rowf

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