



OFFICE OF TOXIC SUBSTANCES  
CODING FORM FOR GLOBAL INDEXING

REV. 7/27/82

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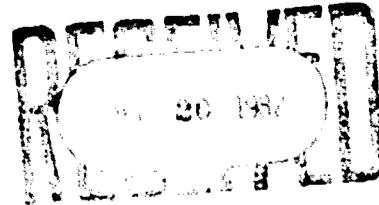


# THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48840

December 9, 1982

Document Control Office  
US Environmental Protection Agency  
TSCA-8D1  
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**OPTS-84003A**

Dear Sir or Madam:

As required by 40 CFR 716, we herewith submit copies of reports which meet the requirements of the referenced rule as Health and Safety Studies. As noted in the statement enclosed with the reports, some contain confidential business information.

The reports are separated into three categories for your convenience.

- Package 1. Reports which contain no Confidential Business Information.
- Package 2. Reports which contain Confidential Business Information.
- Package 3. Reports from which Confidential Business Information has been deleted. (Public File Copy of reports in Package 2).

Each report is marked with an identifying number at the top of the first page of the report, e.g., D-155. Use of this identification number in future correspondence regarding this submission will facilitate handling of questions.

In order to expedite the completion of our search and submission, no attempt was made to determine whether or not we manufactured or processed the chemicals which formed the subject of submitted reports. (40 CFR 716.6). Thus, submission of a report for any given material should not be construed as indicative of Dow's status as a manufacturer or processor of the material.

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Many of the submitted reports contain information which is not relevant to Health or Safety Studies of listed chemicals, e.g., references to unlisted chemicals, marketing or process data, account numbers, internal document identification codes or distribution lists. Such information has been deleted from all copies submitted.

The index required by 40 CFR 716.6(b) is enclosed. It lists the Dow identification number and title of each report submitted in CAS number order. Please note that the index contains Dow Confidential Business Information.

We have also included a reprint of a recently published article dealing with methylene chloride.

Very truly yours,



Robert L. Magerman  
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rt

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D-321 878210967

Biochemical Research Laboratory  
THE DOW CHEMICAL COMPANY

Subject THE TOXICITY OF ANILINE, ANILINE HYDROCHLORIDE,

File No. [redacted]  
Chg. [redacted]  
Rec'd. [redacted]  
File'd 11-20-40  
Work By H. J. Smith, Jr  
V. K. Rowe  
H. C. Spencer  
E. M. Adams

To [redacted] Check *S. D. Smith* 11-27-40 Rept. by *H. C. Spencer*

The results of the toxicological studies made in the Biochemical Research Laboratory are summarized in this report. The detailed experimental data are filed under T27.1-3, T27.1-4, and T27.1-5. Although there are a large number of published articles on the toxicity of these compounds, no attempt is made to summarize the pertinent literature in this report.

Acute Oral Toxicity -- Rats and Cavies

<u>Material</u>	<u>Rats</u>		<u>Cavies</u>	
	100% Survival <u>g./kg.</u>	100% Lethal <u>g./kg.</u>	100% Survival <u>g./kg.</u>	100% Lethal <u>g./kg.</u>
Aniline	0.4	0.6		
Aniline hydrochloride (in terms of aniline)	0.6	1.2		

[redacted]



Chronic Oral Toxicity -- Rats

	Aniline g./kg.	Aniline hydrochloride (in terms of aniline) g./kg.	
Largest quantity survived for twenty doses	0.1	0.1	[REDACTED]
Largest quantity that was fed for 20 doses without producing histopathological changes	0.01	0.001	[REDACTED]
Largest quantity that was fed for 20 doses without causing a change in the blood picture	0.01	0.1 (or greater)	[REDACTED]
Organs in which significant pathological lesions were found.	Blood spleen	spleen kidney	[REDACTED]

Skin Irritation -- Rabbits

Aniline, [REDACTED] and [REDACTED] all produced only a slight simple skin irritation. There was no evidence of a "latent reaction".

Absorption Through the Skin

Aniline, [REDACTED] and [REDACTED] are all absorbed through the skin in sufficient quantity to cause marked systemic poisoning and even death.

Acute toxic absorption experiments with cavies gave the following results:

<u>Material</u>	<u>100% survival dose, g./kg.</u>	<u>100% lethal dose, g./kg.</u>
Aniline	2.4	greater than 3.0
Aniline hydrochloride (in terms of aniline)	3.0 or greater	--

#### Vapor Exposure

No vapor exposure experiments have been made, but numerous published studies indicate that these compounds are quite toxic even in rather low concentrations (ppm).

#### Discussion

The acute and oral toxicities of these compounds are sufficiently low that with "reasonable care" there should be no great danger from these compounds due to oral ingestion. Most certainly "ordinary precautions" should be taken to prevent all possible ingestion of these materials.

These materials do not present a great hazard from skin irritation and, quite probably, no serious skin irritation will be produced if "ordinary precautions" are observed. Quite definitely, there is a much greater danger from absorption of toxic quantities of these materials through the skin with subsequent systemic poisoning, than there is from skin irritation by these materials. Because of this very definite hazard due

to toxic absorption, all possible contact with these materials must be avoided.

An added word of warning should be given, since these materials seriously affect, primarily, the hematopoietic system. Even small doses either ingested orally, inhaled through the respiratory tract, or absorbed through the skin might be expected to produce marked changes in the hematopoietic system.

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Skin Irritation - Rabbits

Twenty applications of the straight material to the inner surface of the rabbit ear over a period of 29 days produced no observable reaction.

Aniline applied to the shaven abdomen for 1/2, 1, or 4 hours produced no reaction; but seven applications of aniline bandaged onto the shaven abdomen over a period of nine days caused moderate hyperemia and slight edema. However, two other rabbits, that received applications of aniline bandaged onto the shaven abdomen, died after 2 and 4 applications, respectively. In both cases the animal became cyanotic before death. Apparently enough aniline was absorbed through the skin to cause systemic poisoning and death.

Judging from these animal experiments, aniline produces only a very slight simple irritation, gives no evidence of a "latent reaction", but is absorbed through the skin in sufficient quantity to produce systemic poisoning.

Aniline probably does not present a serious hazard from the dermatological viewpoint, but most certainly all unnecessary skin contact must be avoided because of its ease of absorption through the skin and its subsequent systemic effects.

Absorption through the skin:

Since two rabbits died after 2-4 applications of aniline were bandaged onto their shaven abdomen, it was considered worthwhile to investigate more extensively the skin absorption of aniline.

Twenty doses of 0.1 g. per kg. aniline caused an appreciable decrease in the number of red blood cells; but the lower concentrations (0.01 or 0.001 g. per kg.) were without effect on the blood picture.

Aniline as the hydrochloride:

Three doses of 0.5 g. per kg. (in respect to aniline) killed a rat, while 0.1 g. per kg. was survived for 20 doses; however, 0.01 g. per kg. for twenty doses still produced very slight hemosiderosis of the spleen. The higher doses produced tubular nephritis as well as definite pigmentary deposits in the spleen. Twenty doses of 0.001 g. per kg. caused no significant histopathological lesions.

No significant blood changes were found in the rats after 20 oral doses of 0.1, 0.01 or 0.001 g. per kg. aniline as the hydrochloride.

Summary of Chronic Oral Experiments - Rats:

	<u>Aniline</u> <u>G./KG.</u>	<u>Aniline hydrochloride</u> <u>(in terms of aniline).</u> <u>G./KG.</u>
Largest quantity survived for twenty doses	0.1	0.1
Largest quantity that was fed for twenty doses without producing histopathological changes	0.01	0.001
Largest quantity that was fed for twenty doses without causing a change in the blood picture	0.01	0.1 (or greater)
Organs in which significant pathological lesions were found	<u>blood</u> <u>spleen</u>	<u>spleen</u> <u>kidney</u>

Blood studies following subcutaneous injection of aniline in a dog:

A dog weighing approximately 25 kg. was anesthetized with chloroform and ether, and then injected subcutaneously with 1.7 cc. aniline. Blood was obtained by heart puncture before the injection, 5 1/2 hours and 8 hours afterwards. There was only a slight decrease in red cells with a corresponding decrease in hemoglobin. The absolute lymphocyte count decreased rather markedly.

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Toxic absorption from one application to the abdomen of a cavy:

A dose of 3.0 g. per kg. aniline applied to the clipped abdomen of cavies, restrained on animal boards, killed one out of five animals; while a dose of 2.4 g. per kg. was survived by five animals.

A dose of 5.0 g. per kg. (in respect to aniline) of aniline hydrochloride in aqueous solution was survived by five cavies. These results may be summarized as follows:

<u>Acute toxic absorption</u>	<u>Aniline</u> <u>g/kg.</u>	<u>Aniline hydrochloride</u> <u>(in terms of aniline)</u> <u>g./kg.</u>
100% survival dose	2.4	3.0 or greater
100% lethal dose	Greater than 3.0	---

Toxic absorption from repeated applications of aniline:

Sixteen applications of 1.0 g. per kg. aniline over a period of 22 days to the clipped abdomen of a cavy caused a slight loss in weight and some evidence of systemic poisoning. However, no histopathological examination was made.

Twenty applications of 0.1 g. per kg. aniline to the shaven abdomen of a rabbit over a period of 29 days caused a slight loss in weight, a slight decrease in the erythrocyte count, and a slight hemosiderosis of the spleen; but twenty similar applications of 0.001 g. per kg. aniline to another rabbit failed to produce any demonstrable effects.

**EXPERIMENTAL DATA**

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline

ACUTE ORAL TOXICITY

Animals Rats



Dose (gm/kilo)	Number of animals that died	Number of animals that survived
0.2	0	5
0.4	0	5
0.6	5	0
0.8	5	0
1.0	1	0
2.0	1	0
3.0	1	0

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline as the hydrochloride

ACUTE ORAL TOXICITY

Animals Rats

(Doses in terms of aniline)

Dose (gm/kilo)	Number of animals that died	Number of animals that survived
0.4	0	3
0.6	0	5
0.8	1	2
1.0	1	2
1.2	5	0

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline

Prob:                     

CHRONIC ORAL TOXICITY

0.5 gm/kilo

Rat # 50 male

Date: 4-21-38

Initial weight 0.200 kg.

Final weight 0.196 kg.

Number of feedings 2 No. days of test                     

General Reaction: Weak and cyanotic. Decapitated.

AUTOPSY

Gross examination:

Blood: Very dark in color.

Spleen: Very dark in color.

General congestion in all organs

Microscopic examination

Liver: (+) Scattered areas of parenchymatous degeneration.

Spleen; (+) Moderate congestion. Slight hemosiderosis.

Kidney: Normal

Adrenal: Slight congestion

Pancreas: Slight congestion

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline

Prob: XXXXXXXXXX

CHRONIC ORAL TOXICITY

0.1 gm/kilo

Rat # 15 male

Date: 4-20-38

Initial weight 0.180 kg.

Final weight 0.205 kg.

Number of feedings 20

No. days of test 29

General Reaction:

Appears normal. Decapitated.

AUTOPSY

Gross examination:

- Blood: Quite dark.
- Spleen: (+) Large and dark.
- All other organs appear normal.

Microscopic examination

- Liver: Normal
- Spleen: (+) Moderate congestion throughout. Slight hemosiderosis.
- Kidney: Normal.
- Adrenal: Normal
- Pancreas: Normal.

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline Prob: XXXXXXXXXX  
CHRONIC ORAL TOXICITY 0.01 gm/kilo  
Rat # 858b female Date: 11-15-38  
Initial weight 0.155 kg. Final weight 0.188 kg.  
Number of feedings 20 No. days of test 30  
General Reaction: Appears normal. Decapitated.

AUTOPSY

Gross examination:

All organs appear normal.

Microscopic examination

Liver: Normal  
Kidney: Normal  
Spleen: Normal  
Adrenal: Normal  
Pancreas: Normal

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline

Prob:                     

CHRONIC ORAL TOXICITY

0.005<sup>gm</sup>/kilo

     Rat # 14      male                     

Date:     4-20-58    

Initial weight     0.184     kg.

Final weight     0.211     kg.

Number of feedings     20    

No. days of test     29    

General Reaction: Normal. Decapitated.

(Injured tongue caused some loss of weight the last few days of the experiment)

AUTOPSY

Gross examination:

All organs appear normal.

Microscopic examination

Liver: Normal

Spleen: Normal

Kidney: Normal

Adrenal: Normal

Pancreas: Normal

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline as the hydrochloride

Prob:                     

CHRONIC ORAL TOXICITY

0.5 gm/kilo

  Rat   #   501     male  

Date:   7-14-38  

Initial weight:   0.219   kg.

Final weight   0.207   kg.

Number of feedings   3  

No. days of test   5  

General Reaction:

Died. Not bled.

AUTOPSY

Gross examination:

Spleen: (+) Large and dark

Kidneys: (++) Cortex light in color - degeneration.

All organs appear congested.

Microscopic examination

Liver: (+) Moderate general congestion. Moderate hemosiderosis. Few scattered areas of focal necrosis, others of hemorrhagic necrosis.

Spleen: (+) Slight congestion. Moderate hemosiderosis.

Kidney: (++) Moderate general congestion. Marked tubular nephritis. Many tubules with completely degenerated epithelium, marked desquamation and sloughing into lumina with consequent distension of lumina and many hyaline casts and much debris. Many nuclei pyknotic. Collecting tubules most seriously affected. Glomeruli essentially normal. (A Kodachrome slide has been made of this kidney section).

Adrenal: Normal.

Pancreas: Normal.

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline as the hydrochloride

Prob:                     

CHRONIC ORAL TOXICITY

0.1 gm/kilo

Rat # 298 male

Date: 7-14-38

Initial weight 0.255 kg.

Final weight 0.274 kg.

Number of feedings 20 No. days of test 29

General Reaction: Apparently normal. Decapitated.

AUTOPSY

Gross examination:

Spleen: (+) Very large and dark.

Otherwise apparently normal.

Microscopic examination

Liver: Normal

Spleen: (+) Moderate congestion. Slight hemosiderosis.

Kidney: (-) Majority of tubules normal - but several with cloudy swelling of epithelium and even desquamation and sloughing with debris and hyaline casts in lumina.

Adrenal: Normal.

Pancreas: Normal.

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline as the hydrochloride

Prob:                     

CHRONIC ORAL TOXICITY

0.01 gm/kilo

   Rat    #   250      male   

Date:   7-14-33  

Initial weight   0.224   kg.

Final weight   0.240   kg.

Number of feedings   20   No. days of test   29  

General Reaction: Normal. Decapitated.

AUTOPSY

Gross examination:

Spleen: (+) Dark in color.

Microscopic examination

Liver: Normal

Spleen: (+) Slight congestion. Very slight hemosiderosis.

Kidney: Normal.

Adrenal: Normal.

Pancreas: Normal.

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline as the hydrochloride Prob:                     

CHRONIC ORAL TOXICITY 0.001 gm/kilo

Rat # 226 male Date: 7-14-33

Initial weight 0.218 kg. Final weight 0.251 kg.

Number of feedings 20 No. days of test 29

General Reaction:

Normal. Decapitated.

AUTOPSY

Gross examination:

Normal

Microscopic examination

Liver: Normal

Spleen: Normal

Kidney: Normal

Adrenal: Normal

Pancreas: Normal

## Summary of Blood Studies on Rats fed Repeated Oral Doses of Aniline

	Rat 15 0.1 G./kg.		Rat 858 b 0.01 G./kg.			Rat 14 0.001 G./kg.	
	4-15-38 Control value	5-17-38 After 20th dose	11-15-38 Control value	12-8-38 After 17th dose	12-13-38 After 20th dose	4-15-38 Control value	5-17-38 After 20th dose
R.B.C. x 10 <sup>6</sup>	7.65	4.51	9.10	8.36	9.33	6.68	7.17
W.B.C. x 10 <sup>3</sup>	14.17	12.5	11.1	14.3	19.7	16.58	18.75
Differential Count: (Percent)							
Neutrophils	14	15	17	19	12	18	15
Lymphocytes	83	82	79	79	84	78	84
Eosinophils	1	1				2	1
Monocytes	2	2	4	2	4	2	
Differential Count: (Absolute)							
Neutrophils	2000	1900	1887	2717	2384	3000	2700
Lymphocytes	11800	10000	8769	11287	16330	12900	15700
Eosinophils	142	125				532	188
Monocytes	284	250	444	286	788	532	

Summary of Blood Studies on Rats Fed Repeated Oral Doses of Aniline Hydrochloride  
(All doses in terms of aniline)

	Rat 298 male 0.1 g./kg.			Rat 230 male 0.01 g./kg.			Rat 226 male 0.001 g./kg.		
	6-25-38 Control value	7-27-38 Before 10th dose	8-10-38 After 20th dose	6-25-38 Control value	7-27-38 Before 10th dose	8-10-38 After 20th dose	6-23-38 Control value	7-27-38 Before 10th dose	8-10-38 After 20th dose
R.B.C. $\times 10^6$	7.11	7.15	7.00	8.49	8.15	9.75	9.09	9.00	9.72
W.B.C. $\times 10^3$	21.6	21.8	17.7	10.7	15.0	14.6	15.8	15.3	24.8
Differential Count: (percent)									
Neutrophils	15	19	28	30	27	25	22	28	29
Lymphocytes	71	69	60	63	57	64	60	57	50
Eosinophils	3	2	5	3	5	3	2	3	4
Monocytes	11	10	7	4	11	8	16	12	9
Differential Count: (Absolute)									
Neutrophils	3240	4140	4960	3210	4050	3650	3480	4290	7190
Lymphocytes	15340	15000	10610	6740	8550	9550	9500	8720	14400
Eosinophils	648	436	885	321	750	458	316	460	995
Monocytes	2380	2180	1240	425	1650	1168	2530	1835	2230

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BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline

Prob.                     

SKIN IRRITATION Abdomen Seven applications of the straight  
material were made to the shaven abdomen over a period of 9 days.

Animal # R-5-191

Date 12-25-37

Day #	Exp.#	Reaction
1	1	
2	2	Slight hyperemia
5	3	" "
6	4	" "
7	5	Slight hyperemia and edema.
8	6	Moderate hyperemia and slight edema.
9	7	" " " " "
12		Exfoliation. Some scab formation.
13		"
14		"
15		Healed.





BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline

~~ACUTE ORAL TOXICITY~~ TOXIC ABSORPTION

Animals Cavies

Dose (gm/kilo)	Number of animals that died	Number of animals that survived
1.0	0	2
2.0	0	2
2.4	0	5
3.0	1	4

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline hydrochloride (aqueous solution)

~~ACUTE-ORAL-TOXICITY~~ TOXIC ABSORPTION

Animals Cavies



(All doses in terms of aniline)

Dose (gm/kilo)	Number of animals that died	Number of animals that survived
1.0	0	1
2.0	0	1
3.0	0	5

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CODING FORM FOR GLOBAL INDEXING

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ANILINE			62-53-3	
ANILINE HYDROCHLORIDE			141-85-5	

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Biochemical Research Laboratory  
THE DOW CHEMICAL COMPANY

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Subject TOXICITY OF ANILINE AND ANILINE HYDROCHLORIDE

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Chg. [redacted]  
Rec'd. 11-11-37  
Filed. 7-24-40  
Work By E. H. Adams  
V. H. Rowe  
E. J. Smith, Jr.  
H. C. Spencer

To [redacted] Check *S. Smith* 9-17-40 Rept. By *H.C.S.*

Summary

Acute Oral Toxicity - Rats:

Aniline:

100% survival dose = 0.4 g. per kg.  
100% lethal dose = 0.6 g. per kg.

Aniline Hydrochloride  
(All doses in terms of aniline)

100% survival dose = 0.6 g. per kg.  
100% lethal dose = 1.2 g. per kg.

Chronic Oral Toxicity:-- Rats:

	<u>Aniline</u> g/kg.	<u>Aniline Hydrochloride</u> (in terms of aniline) g./kg.
Largest quantity survived for twenty doses	0.1	0.1
Largest quantity that was fed for twenty doses without producing histopathological changes	0.01	0.001
Largest quantity that was fed for twenty doses without causing a change in the blood picture	0.01	0.1 (or greater)
Organs in which significant pathological lesions were found	<u>blood</u> <u>spleen</u>	<u>spleen</u> <u>kidney</u>

Skin Irritation - Rabbits:

Aniline produces only a very slight simple skin irritation and gives no evidence of producing a "latent" reaction. No serious skin irritation should be encountered if "ordinary precautions" are observed.

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Absorption through the skin:

Aniline is definitely absorbed through the skin in sufficient quantity to cause marked systemic poisoning and even death.

<u>Acute toxic absorption- Cavies</u>	<u>Aniline g/kg.</u>	<u>Aniline hydrochloride (in terms of aniline) g./kg.</u>
100% survival dose	2.4	3.0 or greater
100% lethal dose	Greater than 3.0	--

Aniline probably does not present a serious hazard from the dermatological point of view, but most certainly all unnecessary skin contact must be avoided because of its ease of absorption through the skin and its subsequent systemic effect.

Blood studies:

Only preliminary studies have been made, but it is evident that aniline, whether administered orally, applied to the skin or injected subcutaneously, causes erythrocyte destruction. A careful comparative study of the blood changes following the different modes of administration would be very interesting.

Material

## I. Aniline

Empirical formula:  $C_6H_7N$

Structural formula:



Formula weight: 95.06  
 Specific gravity: 1.022 20°/4  
 Melting point: -6.2° C.  
 Boiling point: 134.4° C. (handbook)  
 130-131° C. at 742 mm. Hg (uncorrected)  
 Solubilities: Water - slightly soluble  
 Ethanol - soluble  
 Ether - soluble  
 Source: Main Laboratory Stock Room

## II. Aniline hydrochloride

Empirical formula:  $C_6H_8NCl$

Structural formula: 

Formula weight: 129.53  
 Equivalence in terms of aniline:  
 1 g. aniline = 1.39 g. aniline hydrochloride  
 Specific gravity: 1.222 at 4° C.  
 Melting point: 198° C.  
 Boiling point: 245° C.  
 Solubilities: Water - 18 parts per 100 parts water at 15° C.  
 107 parts per 100 parts water at 25° C.  
 Ethanol - soluble  
 Ether - insoluble  
 Source: Main Laboratory Stock Room

### Acute Oral Toxicity - Rats

#### Aniline:

Twenty-three rats were used in this test. Each animal was given one oral dose of aniline dissolved in olive oil and emulsified in gum acacia solution. Those animals that did not die were observed for a period of 4 weeks. It was found that: —

100% survival dose = 0.4 g. per kg.

100% lethal dose = 0.6 g. per kg.

Aniline hydrochloride:

Aniline hydrochloride was administered in water solution and the dose was calculated on the basis of the aniline content so as to be directly comparable with the aniline data. Nineteen rats were used in this test and it was found that:

100% survival dose = 0.6 g. per kg.

100% lethal dose = 1.2 g. per kg.

Apparently aniline as the hydrochloride in water solution is slightly less toxic, orally, than aniline itself in olive oil solution.

Chronic Oral Toxicity - Rats:

Procedure: Rats were given repeated (20) oral feedings of aniline in olive oil or of aqueous aniline hydrochloride solution. The dosage of aniline hydrochloride was in terms of aniline so as to be directly comparable with the aniline data. Blood studies and microscopic examinations of the tissues were made.

Aniline:

Two doses of 0.5 g. per kg. aniline caused marked cyanosis and weakness in a rat, while 20 doses of 0.1 g. per kg. produced no observable signs of intoxication and caused only slight hemosiderosis of the spleen. Twenty doses of 0.01 or 0.001 g. per kg. caused no observable histopathological changes. The pathological changes noted in the spleen and blood were the only lesions of consequence encountered in these rats.

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline

Prob:                     

CHRONIC-ORAL-TOXICITY TOXIC ABSORPTION

1.0 gm/kilo

Cavy # 56 female

Date: 12-15-57

Initial weight 0.351 kg.

Final weight 0.342 kg.

applications

Number of feedings 16

No. days of test 22

General Reaction:

                    Appeared to have lost voice near end of  
experiment. Killed.

AUTOPSY

Gross examination:

                    No examination

Microscopic examination

                    No examination.

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline

Prob: XXXXXXXXXX

CHRONIC ~~ORAL-TOXICITY~~ TOXIC ABSORPTION

0.1 gm/kilo

Rabbit # 5-516

Date: 2-8-58

Initial weight 2.71 kg.

Final weight 2.67 kg.

applications

Number of feedings 20 No. days of test 29

General-Reaction: Method: Measured quantity applied to abdomen and kept wet (hourly) with 95% ethanol. 5 hour daily exposures made. General Reaction: Appears normal

AUTOPSY

Gross examination:

Organs appear normal

Microscopic examination

Liver: Normal

Spleen: (+) Slight congestion. Slight hemosiderosis.

Kidney: Normal

Adrenal: Normal

BIOCHEMICAL RESEARCH LABORATORY

Material: Aniline (1% solution in 95% ethanol) Prob: XXXXXXXXXX

CHRONIC ORAL TOXICITY TOXIC ABSORPTION 0.001gm/kilo

Rabbit # 5-514 Date: 2-3-38

Initial weight 2.26 kg. Final weight 1.90 kg.

applications

Number of feedings 20 No. days of test 29

General Reaction: Appears normal. Weight loss probably due to restraint on animal board.

Method: Measured amount applied to abdomen and kept wet (hourly) with 95% ethanol. 5 hour daily exposures made.

AUTOPSY

Gross examination:

Animal thin. Organs appear normal.

Microscopic examination

Liver: Normal

Spleen: Normal

Kidney: Normal

Adrenal: Normal

Pancreas: Normal

Summary of the Blood Studies on Rabbits that Received Repeated Applications of Aniline to the Shaven Abdomen

<u>Blood Constituents</u>	2-7-38 Control value	R-5-516 0.1 G./kg.			2-7-38 Control value	R-5-514 0.001 G./kg.		
		2-15-38 6th dose	2-25-38 12th dose	3-7-38 20th dose		2-15-38 6th dose	2-25-38 12th dose	3-7-38 20th dose
R.B.C. x 10 <sup>6</sup>	5.96	6.59	5.35	4.90	6.17	5.23	5.46	5.97
W.B.C. x 10 <sup>3</sup>	12.7	8.65	5.60	7.30	6.70	8.45	12.75	8.50
Differential Count:								
(Percent)								
Neutrophils		48	25	37		51	23	23
Lymphocytes		52	71	57		49	66	68
Monocytes			2	1		1	3	2
Basophils			2	5			3	2
Differential Count:								
(Absolute)								
Neutrophils		4150	1400	2700		4310	3570	2580
Lymphocytes		4500	5980	4160		4060	8415	5780
Monocytes			112	75		85	585	170
Basophils			112	365			585	170
Hemoglobin:								
G./100 cc	15.0	12.8	13.2	13.3	13.0	9.9		11.8
Percent	104	88.3	91.0	91.7	89.6	69.3		81.4

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Summary of Blood Studies on a Dog Following Subcutaneous Injection of 1.7 cc. Aniline. (Dog anesthetized with chloroform and ether - blood obtained by heart puncture)

<u>Blood Constituents</u>	<u>Before injection</u>	<u>5 1/2 hours after injection</u>	<u>6 hours after injection</u>
Appearance of blood	Normal	Dark red	Dark red
R.B.C. $\times 10^6$	6.99	6.87	5.53
Hemoglobin:			
g./100 cc.	15.0	14.6	12.8
Percent	104	101	88.3
W.B.C. $\times 10^3$	10.5	10.7	7.2
Differential Count:			
(In percent)			
Neutrophils	70	87	91
Lymphocytes	26	11	7
Eosinophils	3	1	
Monocytes	1	1	2
Differential Count:			
(Absolute per cu. mm)			
Neutrophils	7350	9310	6550
Lymphocytes	2730	1180	504
Eosinophils	315	107	
Monocytes	105	107	140

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REV. 7/27/82

Microfiche No. (7) •	206127	No. of Pages	2
Doc I.D.	878211146	3 Old Doc I.D.	8DS
Case No.(s)	OTS 84003A	11	5
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		Conf. Code •	8 N
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Pub/Journal Name	9		
	9		
Author(s)	10		
Organ. Name	11 DOW CHEM CO		
Dept/Div	12		
P.O. Box	13	Street No./Name	14
City	15 MIDLAND	State	16 MI
		Zip	17 48640
		Country	18
MID No. (7)	19 0010264	D & B NO. (11)	20 0013-815-81
Contractor	21		
Doc Type	22 •RI•UP•HEAS• 8D SU HS FN		
Doc Title	23 RESULTS OF RANGE FINDING TOXICOLOGICAL TESTS ON 2,4,6-TRIBROMOANILINE		
Chemical Name (300 per name)	25 ANILINES	CAS No. (10)	24 99999994
	2,4,6-TRIBROMOANILINE		47-82-0

5/26

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D-229

878211146

Biochemical Research Department

THE DOW CHEMICAL COMPANY

SUBJECT: RESULTS OF RANGE FINDING TOXICOLOGICAL TESTS ON 2,4,6-TRIBROMOANILINE

File

Chg.

Rec'd. 7-31-52

Fin'd. 4-28-53

Rept. By

Signed

Date 5-7-53

Checked

Date 5-8-53

To

THIS REPORT IS THE PROPERTY  
OF  
THE DOW CHEMICAL COMPANY

UNIT INDEX

2,4,6-Tribromoaniline has a low acute oral toxicity, is mildly irritating to the eyes and only slightly so to the skin. It presents no unusual hazards, therefore, it may be handled safely if safety glasses and good habits of personal cleanliness are used.

INDEX HEADINGS

2,4,6-Tribromoaniline

Aniline: 2,4,6-tribromo-,

PROBLEM

This material is being sent outside the company. What are its hazards and what precautions must be observed to insure its safe handling?

Biochemical Research Department

Page 2

CONCLUSIONS

2,4,6-Tribromoaniline has a low acute oral toxicity, is mildly irritating to the eyes and only slightly so to the skin. It presents no unusual hazards, therefore, it may be handled safely if safety glasses and good habits of personal cleanliness are used.

SAMPLE INFORMATION

C.R.I. Name: Aniline: 2,4,6-tribromo-,

Common Name: 2,4,6-Tribromoaniline

Source:

Reference: 100-3A SSR#118-533

Melting Point: 121°C.

K No.:

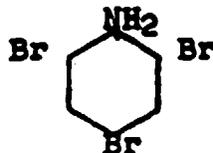
Date Sample Received: 7-31-52

Physical State: White powdery solid

Solubility: Acetone

Molecular Formula: C<sub>6</sub>H<sub>4</sub>Br<sub>3</sub>N

Structural Formula:



SUMMARY OF RANGE FINDING TOXICOLOGICAL DATA

Acute Oral Toxicity

<u>Animal</u>	<u>Preparation Fed</u>	<u>Dose (g/kg)</u>	<u>No. Died</u> <u>No. Fed</u>	<u>Response-Remarks</u>
Cavy	20% in corn oil	2.00	0/2	Killed after 12 days observation.

000003

Eye Irritation - Rabbit

<u>Material</u>	<u>Treatment</u>	<u>Response-Remarks</u>
100%	Unwashed	Slight conjunctival irritation and trace of corneal injury healed in 24 hours.
100%	Washed	Trace of response, healed in 48 hours.

Skin Irritation - Rabbit

<u>Material</u>	<u>Condition of Skin</u>	<u>No. of Appl.</u>	<u>Site</u>	<u>Response-Remarks</u>
100%	Intact	10	Belly	Trace of response.
100%	Abraded	5	Belly	Healed well.

SUMMARY OF HAZARDS

Oral

2,4,6-Tribromoaniline has a low acute oral toxicity. There is no problem from ingestion incidental to the handling and use of this substance. If large quantities were swallowed, accidentally or willfully, some injury might result; the likelihood of serious injury is remote.

Eye

2,4,6-Tribromoaniline presents a slight hazard from contact with the eye. Pain and conjunctival inflammation may persist for several days. Transient corneal injury may occur, but is expected to heal completely within a few days.

## Biochemical Research Department

Page 4

Skin

2,4,6-Tribromoaniline is very slightly irritating to intact and abraded skin. Prolonged or repeated contact may be expected to result in some very slight effect.

Absorption

2,4,6-Tribromoaniline is not absorbed through the skin to any appreciable extent.

PRECAUTIONS FOR SAFE HANDLING AND USE

This material presents no unusual hazards. It may be handled safely if safety glasses are worn and good personal cleanliness is practiced.

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Microfiche No. (7) •		206127		1		No. of Pages		2		
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Doc Title										
RESULTS OF TOXICOLOGICAL TESTS ON										
O-CHLORO-P-NITRANILINE (OCPN)										
Chemical Name (300 per name)					25		CAS No. (10)		24	
ANILINES							999999994			
O-CHLORO-P-NITRANILINE							121-87-9			

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878211147

D-182

Biochemical Research Department  
THE DOW CHEMICAL COMPANY

Office Copy

Subject: RESULTS OF TOXICOLOGICAL TESTS  
ON o-CHLORO-p-NITRANILINE  
(OCPN)

File  
Chg.  
Rec'd. 4-5-51  
Fin'd. 8-20-52  
Report by F. Oyen

Signed F. Oyen Date 1-2-52 Checked W. Kowal Date 8-26-52

UNIT INDEX

o-Chloro-p-nitraniline is slightly irritating to the skin.  
It may be absorbed through the skin from excessive, prolonged  
contact. It is slightly toxic upon repeated ingestion.

00002

INDEX HEADINGS

o-Chloro-p-nitraniline

Aniline: 2-chloro-4-nitro-,  
OCPN

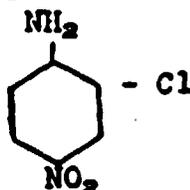
PROBLEM:

Toxicological data were needed to permit a more definite evaluation of the hazard of workmens' exposures.

SAMPLE INFORMATION

C. R. I. Name: o-Chloro-p-nitraniline

Structural Formula:



Molecular Formula:  $C_6H_5ClN_2O_2$

B. R. D. K. No.:

Source: C. Landis

Physical State: M. P. 105°C. Yellow Solid.

EXPERIMENTAL RESULTS

Acute Skin Absorption: Single doses of the material were placed in a cuff around the shaven trunk of the rabbit for 24 hours. Results are tabulated below:

<u>Dose</u>	<u>Preparation</u>	<u>Absorption</u>	<u>Mortality</u>	<u>Response</u>
3 g./kg.	50% Dowanol 50B	Slight	None	Slightly cyanotic and slight necrosis; moderate skin irritation.
3 g./kg.	50% Water Slurry	Slight	None	Possible cyanosis, sl. skin irritation.
1 g./kg.	50% Dowanol 50B	Slight	None	Moderate skin irritation.
1 g./kg.	50% Water Slurry	Slight	None	Slight skin irritation.

000003

Skin Irritation Tests:

The solid material and a 10% solution in Dowanol 5CB were tested by applying to the ear and shaven belly of a rabbit five days a week for two weeks. The solid material elicited a very slight irritation on the belly. The 10% solution elicited a slight irritation on the belly, but only a very slight irritation on the ear.

Short Term Dietary Feeding:

Male rats (6 per group) were maintained for 118 days on diets containing 0.00 (control), 0.01, 0.03, 0.10, 0.30, 1.00 and 3.00 per-cent o-chloro-p-nitroaniline.

The animals receiving 3.00 percent OCPN exhibited a marked depression of growth due in part, at least, to poor acceptability of the experimental diet as indicated by food consumption records. All of the rats survived the experimental period. Microscopic examination revealed slight degenerative changes in the liver, and moderate to marked changes in the kidney, spleen, and testes. In the kidney, there were varying degrees of degeneration of the tubular epithelium with concomitant cast formation and distention of the lumina. The spleen showed marked congestion and an engorgement of the phagocytes with a yellow-brown material. In spite of considerable testicular atrophy and varying degrees of degenerative changes in the germinal tissue, there was still ample evidence of spermatogenesis in all sections of testes examined.

The group of rats receiving the diet containing 1.00 percent OCPN exhibited a moderate retardation of growth in conjunction with a poor food consumption record. None of the animals died during the experimental period. Terminal red and white blood cell counts,

000004

differential white cell counts and hemoglobin values were normal. Microscopic examination revealed only slight kidney damage, and slight to moderate changes in the spleen and testes.

The group of rats receiving the diet containing 0.30 percent OCPN showed no evidence of adverse effect as judged gross appearance and behavior, mortality, food consumption, final organ weights, and gross examination at autopsy. However, there was a slight depression of growth and microscopic examination of the tissues revealed very slight changes in the spleen and testes.

The groups of male rats that were maintained for 118 days on diets containing 0.10, 0.03 and 0.01 percent o-chloro-p-nitroaniline showed no evidence of adverse effects as judged by gross appearance and behavior, growth, mortality, food consumption, final body and organ weights, and gross and microscopic examination of the tissues.

#### CONCLUSIONS

With certain conventional assumption, it may be calculated that a concentration of 0.10% in the diet of rats is comparable to an intake for human subjects of about 2500 mg. per day.

In regard to atmospheric contamination, assuming the daily inhalation of  $10 \text{ m}^3$  of air and 100% retention of inhaled dust, this daily intake may be represented by a concentration in air of  $250 \text{ mg./m}^3$ . In transferring animal data to human subjects, a safety factor is advisable because of unpredictable variations in susceptibility between species. Application of a factor of 10 yields a concentration of  $25 \text{ mg./m}^3$ , a concentration that may be used for evaluating workmens' exposures.

Absorption through the skin does occur, but is very slow. It can be a cause of concern only for extensive, prolonged and repeated

000005

skin contacts.

#### SUMMARY OF HAZARDS

##### o-Chloro-p-nitroaniline is Only Very Slightly Absorbed Through the Intact Skin

The hazard from absorption in ordinary industrial operation is not great. Sufficient material, however, may enter the body during a severe, prolonged exposure to produce cyanosis and narcosis.

##### o-Chloro-p-nitroaniline is Very Slightly Irritating to the Skin

The solid material should present no hazard in industrial operations except from prolonged and repeated contacts.

##### o-Chloro-p-nitroaniline Has a Low Systemic Toxicity

The hazard from ingestion in ordinary industrial operations is not great. Calculations indicate excessive inhalation and ingestion may result only from atmospheric concentrations greater than 25 mg./m<sup>3</sup>.

#### PRECAUTIONS FOR SAFE HANDLING AND USE

Precautions should be taken to avoid repeated and prolonged skin contact with the material. Since it is a yellow dye, the mere presence of color does not indicate an excessive exposure.

Measures should be taken to keep atmospheric contamination below 25 mg./m<sup>3</sup>.

Respiratory protection should be utilized for appreciable contact with higher concentrations.

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Microfiche No. (7) •	206127	1	No. of Pages	2
Doc I.D.	878211148	3	Old Doc I.D.	8DS
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Pub/Journal Name				9
Author(s)				10
Organ. Name	DOW CHEM CO			11
Dept/Div				12
P.O. Box		13	Street No./Name	14
City	MIDLAND	15	State	MI 16
			Zip	4864φ 17
			Country	
MID No. (7)	φφ1φ266	19	D & B NO. (11)	φφ13-815-81
Contractor				21
Doc Type	• R I • U P • H E A S D 8 D . S U H S F N			22
Doc Title	PRELIMINARY EXPERIMENTS ON THE ACUTE ORAL TOXICITY OF ORTHO-CHLORO-PARA-NITRANILINE			23
Chemical Name (300 per name)	ANILINES		CAS No. (10)	999999994
	ORTHO-CHLORO-PARA-NITRANILINE			121-87-9

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D-174

87821148

June 18, 1941

**Biochemical Research Laboratory**

**ORTHO-CHLORO-PARA-NITRANILINE :**

**Summary:**

Preliminary experiments in this laboratory have shown that the acute oral toxicity of ortho-chloro-para-nitraniline is rather low and that even rather large repeated oral doses can be given without causing serious systemic effects. No information is available concerning its effect upon the skin except the statement by Schwartz and Tulipan that it should be classified as a skin irritant.

It is believed that this material presents no serious hazard if reasonable care is taken to prevent skin contact.

**Data and Discussion:**

Preliminary work in this laboratory has shown that the acute oral toxicity of ortho-chloro-para-nitraniline is rather low. In large doses it apparently has a marked narcotic effect. The following results were obtained by single oral feedings to cavies:

100% survival dose = 0.5 grams per kilogram  
100% lethal dose = 1.6 grams per kilogram

It was also found that repeated feedings of 0.1 gram per kilogram could be given to a rabbit for 23 doses over a period of 31 days without causing serious systemic effects.

No significant study of the effect of ortho-chloro-para-nitraniline upon the skin has been made in this laboratory. There is apparently very little data in the literature concerning this compound. Schwartz and Tulipan (A Textbook of Occupational Diseases of the Skin, Lea and Fibiger, Philadelphia, 1939, page 742) list this material among the "chemicals which are known to be or which can be skin irritants." However, the absence of other reports on ortho-chloro-para-nitraniline probably indicates that very little actual trouble has been encountered in the handling of this material.

Until more information is available concerning the effect of ortho-chloro-para-nitraniline upon the skin, and in view of the statement by Schwartz and Tulipan, this material should be considered as a possible skin irritant and handled accordingly.

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Microfiche No. (i) •	206127	1	No. of Pages	2
Doc I.D.	878211355	3	Old Doc I.D.	835
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Pub./Journal Name				9
Author(s)				10
Organ. Name	DOW CHEM CO			11
Dept/Div				12
P.O. Box	13	Street No./Name	14	
City	MIDLAND	15	State	MI
		16	Zip	48640
		17	Country	
MID No. (7)	0017200	19	D & B NO. (11)	0013-815-81
Contractor				21
Doc Type	• R.I. • U.P. • H.E.A.S.D. 8.D. S.G. H.S. F.N.			22
Doc Title	RANGE FINDING ACUTE ORAL STUDIES CONDUCTED ON 39 POLYHALOGEN SUBSTITUTED SALICYLANILIDES EMPLOYING LABORATORY MICE			23
Chemical Name (300 per name)	25		CAS No. (10)	24
ANILINES			999999994	
SALICYLANILIDES			81-17-2	
3,4-DICHLOROANILINE			95-76-1	

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Biochemical Research Laboratory

The Dow Chemical Company

RANGE FINDING ACUTE ORAL STUDIES  
CONDUCTED ON 39 POLYHALOGEN SUB-  
STITUTED SALICYLANILIDES  
EMPLOYING LABORATORY MICE

File  
Ref. See below  
Sub. By  
Rept. By H. Wilson  
K. J. Olson

Signed Hellie Wilson 5/24/66

*Hellie Wilson 5/2/66*

Signed K. J. Olson, May 27, 1966

*K. J. Olson  
5/3/66*

Checked F. Olson 5-27-66

DISTRIBUTION

CRI

PURPOSE

The purpose of this project was to evaluate the range of acute oral toxicity for the subject materials.

METHOD

Two mice were employed on each dose level administered. The materials were administered by single-dose gavage as aqueous solutions employing in some cases a 0.5% gum arabic solution to assist in providing a suitable suspension. The mice weighed approximately 20-25 grams and were fasted overnight prior to feeding and for two hours thereafter unless otherwise indicated. All animals were observed for two weeks. The dose levels used ranged from 0.031 to 2.0 grams per kilogram body weight.

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RESTRICTED: for use within The Dow Chemical Company only.

<u>Material</u>	<u>K Number</u>	<u>% Of Suspension Or Solution Fed</u>	<u>Range Of LD<sub>50</sub> (g/kg)</u>	<u>Response: 0-24 hours</u>
3,4-Dichloro- aniline	2986*	10% suspension	>2.0	<b>Immediate:</b> Normal. <b>1 Hour:</b> All were slightly depressed. <b>2 Hours:</b> Only one animal on 0.252 dose was depressed; others normal. <b>24 Hours:</b> All normal.

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Materials were fed in water solution, unless (\*) denoting 0.5% gum arabic solution. Mice weighed approximately 20-25 grams, were starved overnight pre-feeding and for two hours post-feeding. Mice were observed for two weeks.

+ Not fasted.

Material	<u>K Number</u>	% Of Suspension Or Solution Fed	Range Of <u>LD<sub>50</sub></u> (g/kg)	<u>Response: 0-24 hours</u>
----------	-----------------	--	---	-----------------------------

3,5-Dichloro-aniline	51607*	10% suspension	>2.0	<p>Immediate: Normal.</p> <p>1 Hour: Animals on 2.0 dose had an unusual dragging gait.</p> <p>2 Hours: One mouse on 2.0 was prostrate, almost dead.</p> <p>24 Hours: Survivors normal.</p>
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OFFICE OF TOXIC SUBSTANCES  
CODING FORM FOR GLOBAL INDEXING

REV 7/27/82

Microfiche No. (7) •	206127	1	No. of Pages	2
Doc I.D.	878211356	3	Old Doc I.D.	8DS
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Pub/Journal Name				9
				9
Author(s)				10
Organ. Name	DOW CHEM CO			11
Dept/Div				12
P.O. Box	13	Street No./Name	14	
City	MIDLAND	15	State	MI
		16	Zip	48647
		17	Country	
MID No. (7)	001026U	19	D & B NO. (11)	0013-815-81
Contractor				21
Doc Type	• R.T. • U.P. • HEADS D. • S.U. H.S. F.N.			22
Doc Title	THE DETERMINATION OF 3,4-DICHLOROANILINE			
	(3,4-DCA) IN WATER BY HIGH			
	PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)			
Chemical Name (300 per name)	25	CAS No. (10)	24	
ANILINES		999999994		
3,4-DICHLOROANILINE		95-76-1		

5B  
5P6  
1A

87821/356  
- 345

THE DETERMINATION OF 3,4-DICHLOROANILINE (3,4-DCA)  
IN WATER BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

ES-429  
April 24, 1981

by

Tim D. Lickly  
Environmental Sciences Research Laboratory  
Dow Chemical U.S.A.  
Midland, Michigan 48640

Date Test Started: 1/26/81  
Date Test Completed: 2/4/81

ABSTRACT

A high performance liquid chromatographic (HPLC) method was developed to monitor the concentration of 3,4-dichloroaniline (3,4-DCA) in water for a photolysis study of the title compound. Separation was on a reverse phase isocratic system using a microparticulate C18 column and a 67.5/32.5 (v/v) methanol-water eluent. Detection was by UV at 240 nm. Detector response was linear over a concentration range of 0.1 to 1.0 ppm. Replicate consecutive analyses (three times) of a single concentration showed a relative precision of  $\pm 4\%$  (2 S.D.) at the 0.2 ppm level. Relative precision ranged from  $\pm 1\%$  to  $\pm 4\%$  (2 S.D.) for the 0.2 to 1.0 ppm concentration range for three replicate analyses.

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## INTRODUCTION

The environmental fate of compounds exposed to sunlight in aqueous media at any longitude or latitude in any season can be predicted by determining the compound's quantum yield in aqueous media and utilizing this information in the U.S. Environmental Protection Agency's EXAMS environmental mode (1). Environmental Sciences Research has recently set up an apparatus for determining a compound's quantum yield. This report describes the high performance liquid chromatography (HPLC) method that was used in conjunction with the quantum yield determination of 3,4-dichloroaniline (3,4-DCA) by L. C. Lickly (2).

## EXPERIMENTAL

Earlier work by Milles et al (3) described a method for the extraction with benzene of aqueous solutions containing ~1 ppm levels of 3,4-DCA and subsequent quantitation by gas chromatography with electron capture detection (GC/EC). Miller also described a method for the separation of higher concentrations of 3- and 4-chloroaniline by reverse phase HPLC. Because of the convenience of aqueous direct injections into a HPLC system which eliminates the solvent extraction recovery procedures essential for a gas chromatographic method, the HPLC method was pursued.

### Analytical Conditions

The instrument used for this study was a Hewlett Packard Model 1084B HPLC equipped with a variable wavelength detector. This instrument, as set up, was equipped with both a Rheodyne injector and a Hewlett Packard variable volume injector and auto-sampler. Initial exploratory studies were conducted with the Rheodyne injector equipped with a 20  $\mu$ L loop, but for optimization of the method, for the final linearity studies and all experimental determinations, the variable volume injector set at 40  $\mu$ L was used. This setting was the maximum injection volume observed that didn't appear to distort the peak shape. The wavelength monitored was 240 nm, the wavelength of maximum U.V. absorption for 3,4-DCA (Figure 1). The column used was a DuPont Zorbax<sup>®</sup> ODS with the eluent consisting of MeOH/H<sub>2</sub>O. The eluent composition ranged from 65% to 70% MeOH (by volume), with final determinations made using an eluent consisting of 67.5% MeOH, 32.5% water, at a flow rate of 1.5 mL/min. This gave a retention time for 3,4-DCA of ~4.5 min. Minor changes in the eluent composition had tremendous effects on the retention time of 3,4-DCA. Figure 2 shows chromatograms for a standard and a sample.

### Linearity Study

Initially, all standards were made up in 100% MeOH and a linearity study done on the methanol solutions. Discrepancies between the assumed nominal concentration of a water solution of 3,4-DCA and the result of analysis as compared to the MeOH standards, prompted the linearity study to be rerun using standards made up of ~0.5% MeOH in water. While the detector response to both sets of standards was linear over the concentration range studied, the detector response was dramatically different for the water and MeOH standards, based on peak height measurements (Figure 3). The standards in water had a much sharper peak shape than the standards in MeOH. The detector response was similar for the water and MeOH standards based on peak area (Figure 4), but the reproducibility of the area values at low concentrations (0.1 ppm) was not as good as the reproducibility of the peak height at these low levels. This was apparently due to instrument variability in determining the integration baseline with small, sporadically tailing peaks as was observed at the 0.1 ppm level.

### Precision Study

At least three replicate injections of the 3,4-DCA standards (in water) were made at each concentration. The concentration range of the standards spanned the range of interest for the photodegradation study. Nine replicate injections at 0.4 ppm and twelve replicate injections at 0.8 ppm were made over the two-day period when the samples from the photolysis study were analyzed. Table 1A shows the results for the replicate injections by peak height. These values have a relative precision of ~±4% (2 S.D.) at 0.2 ppm; ~±1% (2 S.D.) at 1.0 ppm. This table also shows the relative precision of the nine and twelve injections of the 0.4 ppm and 0.8 ppm solution respectively, to be similar, indicating no greater precision was obtained from increasing the number of injections. Table 1B shows the results for the same set (run) of standards based on peak area. By peak area, the values have a relative precision of ~±5% at 0.2 ppm; ~±5% at 1 ppm. In these determinations using peak area similar precision was obtained from nine or twelve replicate injections. All subsequent determinations were made based on 3 replicate injections with peak height measurement because of apparent instrument variability in determining the integration baseline at the 0.1 ppm level. A response factor for 3,4-DCA (by peak height) was generated from all the standards on Table 1A (which were run during the photolysis measurements). This data was also used to show the detector's linearity response to 3,4-DCA. A graph of this data (including a line of best fit) is displayed in Figure 5.

## RESULTS

Table 2 shows the results for the three replicate injections (in peak height units, mm) for the hydrolysis (0-HR HYDRO and 2 HR HYDRO) and the duplicate photolysis samples. The 2-hr hydrolysis sample was actually analyzed as the last sample in the series, ~10 hours after it was removed from the water bath. Table 3 shows the mean peak height for the three replicate analyses and the resulting final concentrations for the samples.

## DISCUSSION

The comparison of the peak height and the peak area precision in the Precision Study section indicates the problems observed with this detector at the 0.1 ppm level. The instrument appeared to have problems determining the integration interval, leading to low precision at this level based on peak area. The peak height method seemed very precise in comparison.

During this study the solvent matrix for the standards was shown to have a dramatic effect on the interpretation of the result (See Figure 3), indicating the precautions to be taken on this point in other studies.

One technical problem observed with the Hewlett Packard 1084B HPLC was that when using both pumps to deliver a mixed eluent, the UV baseline observed was much more unstable than pre-mixing the eluent and using one pump to deliver the pre-mixed eluents (Figure 6).

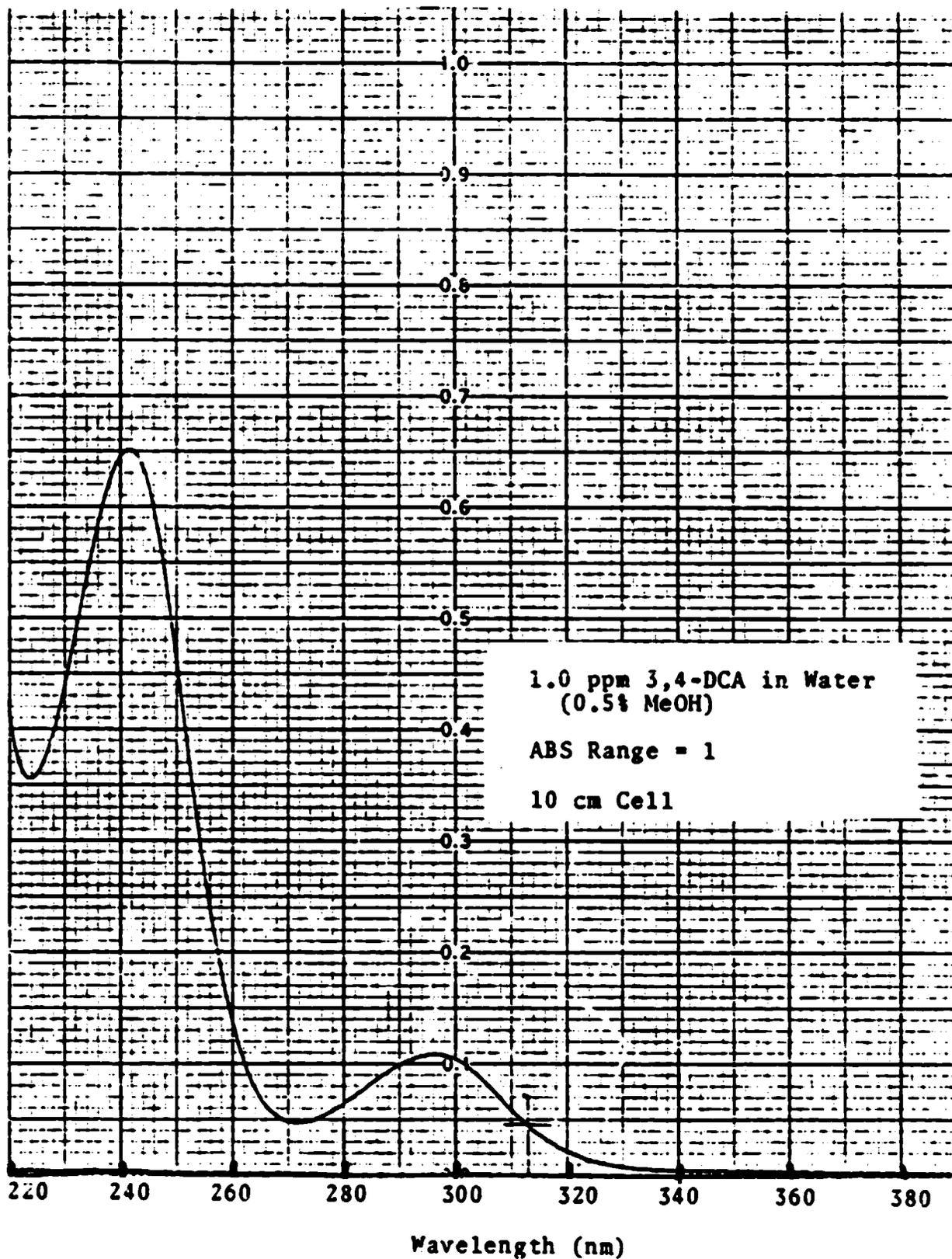
## CONCLUSIONS

A liquid chromatography method has been developed and used for the determination of 3,4-dichloroaniline at levels of 0.1 ppm to 1.0 ppm in aqueous solutions. The method, using the Hewlett Packard Model 1084B HPLC system equipped with a variable volume injector, autosampler, and variable wavelength UV detector, proved to be fast, precise and required little analyst time for the determinations.

REFERENCES

1. Burns, L. A., Draft EXAMS Model, U.S. EPA, Athens, Georgia.
2. Lickly, L. C., Work on quantum yield determinations of Chlorpyrifos and Trichloropyridinol in progress.
3. Miller, G. C., Mille, M. J., Crosby, D. G., Sintum, S. and Zepp, R. G., "Photosolvolysis of 3,4-Dichloroaniline in Water," Tetrahedron, Vol. 35, pp. 1797-1800.

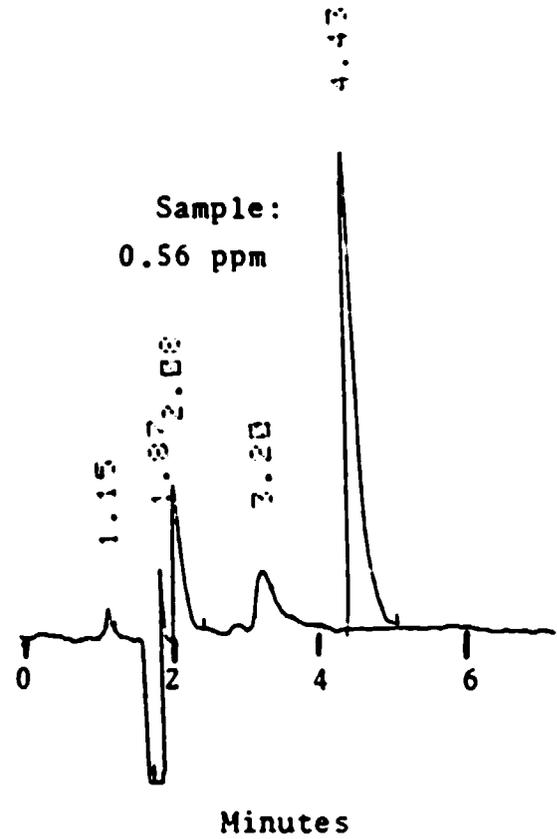
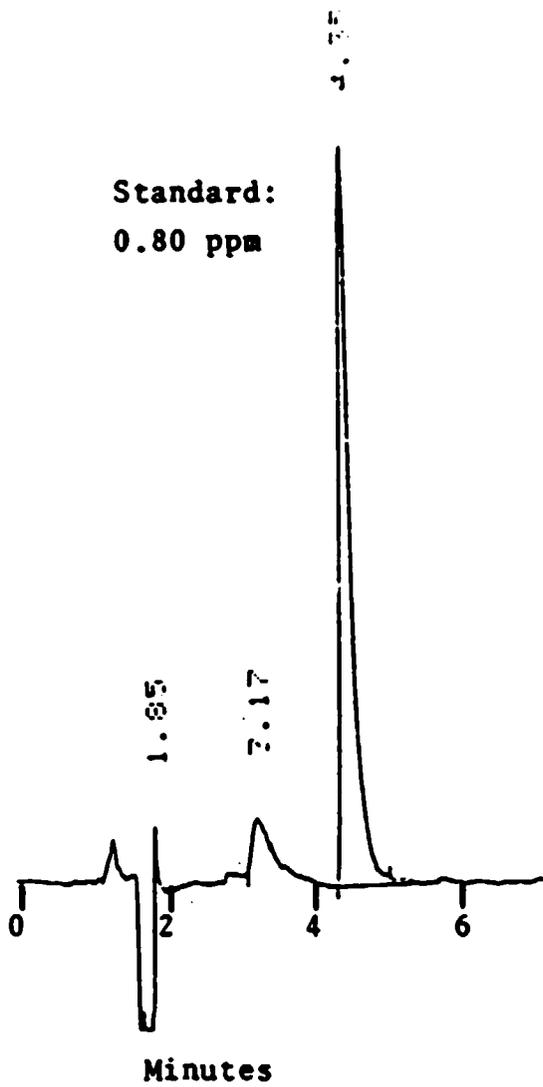
**FIGURE 1.** Ultraviolet Spectrum of 3,4-Dichloroaniline



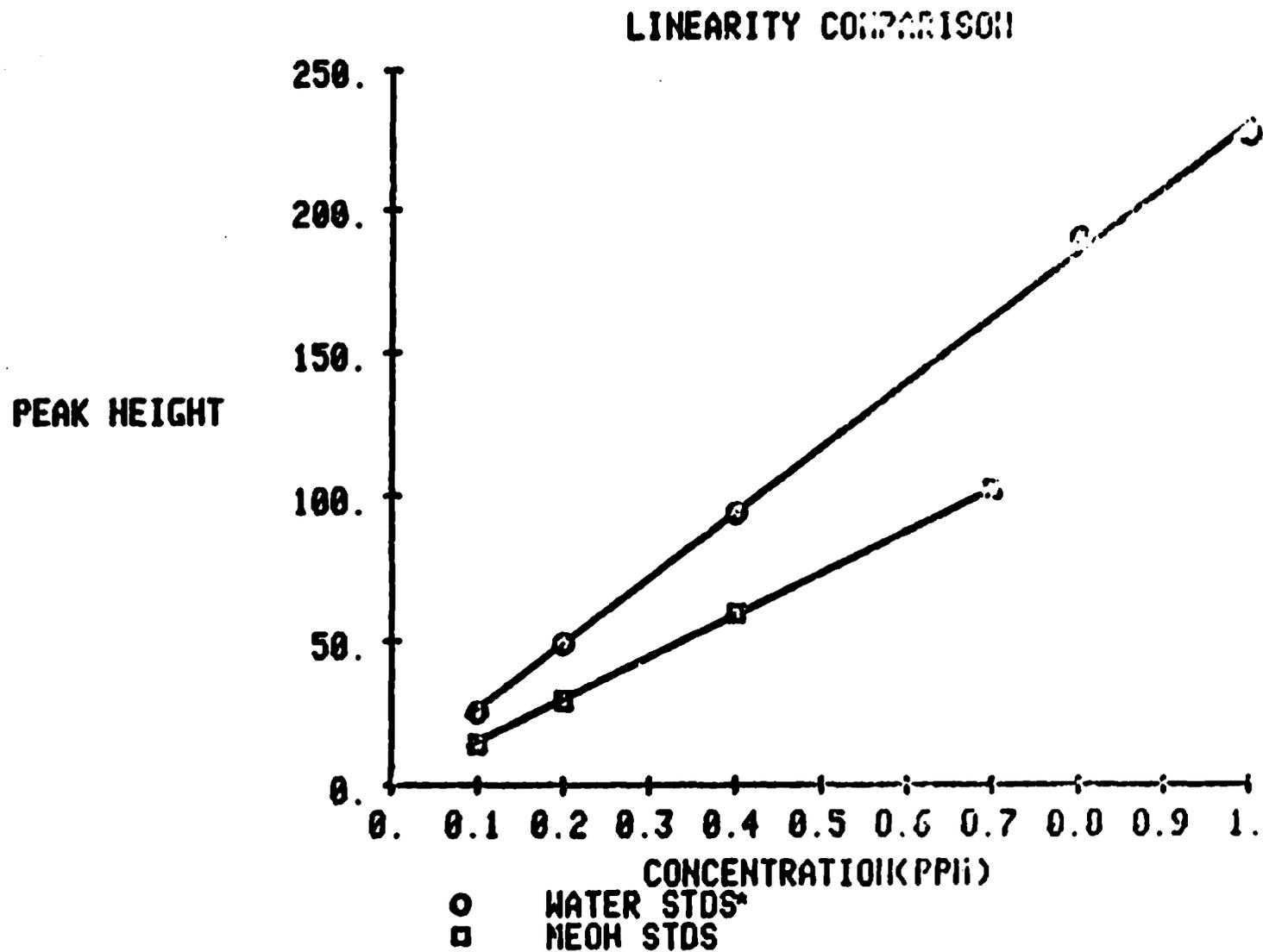
**FIGURE 2.** Chromatograms from HPLC Determination of 3,4-DCA

**Analytical Conditions**

Instrument: Hewlett Packard 1084B  
Column: Zorbax® ODS -- 4.6 mm x 25 cm  
Eluent: 67.5% MeOH/32.5% H<sub>2</sub>O  
Flow Rate: 1.5 mL/min  
Detection: UV @ 240 nm  
Injection Volume: 40 µL



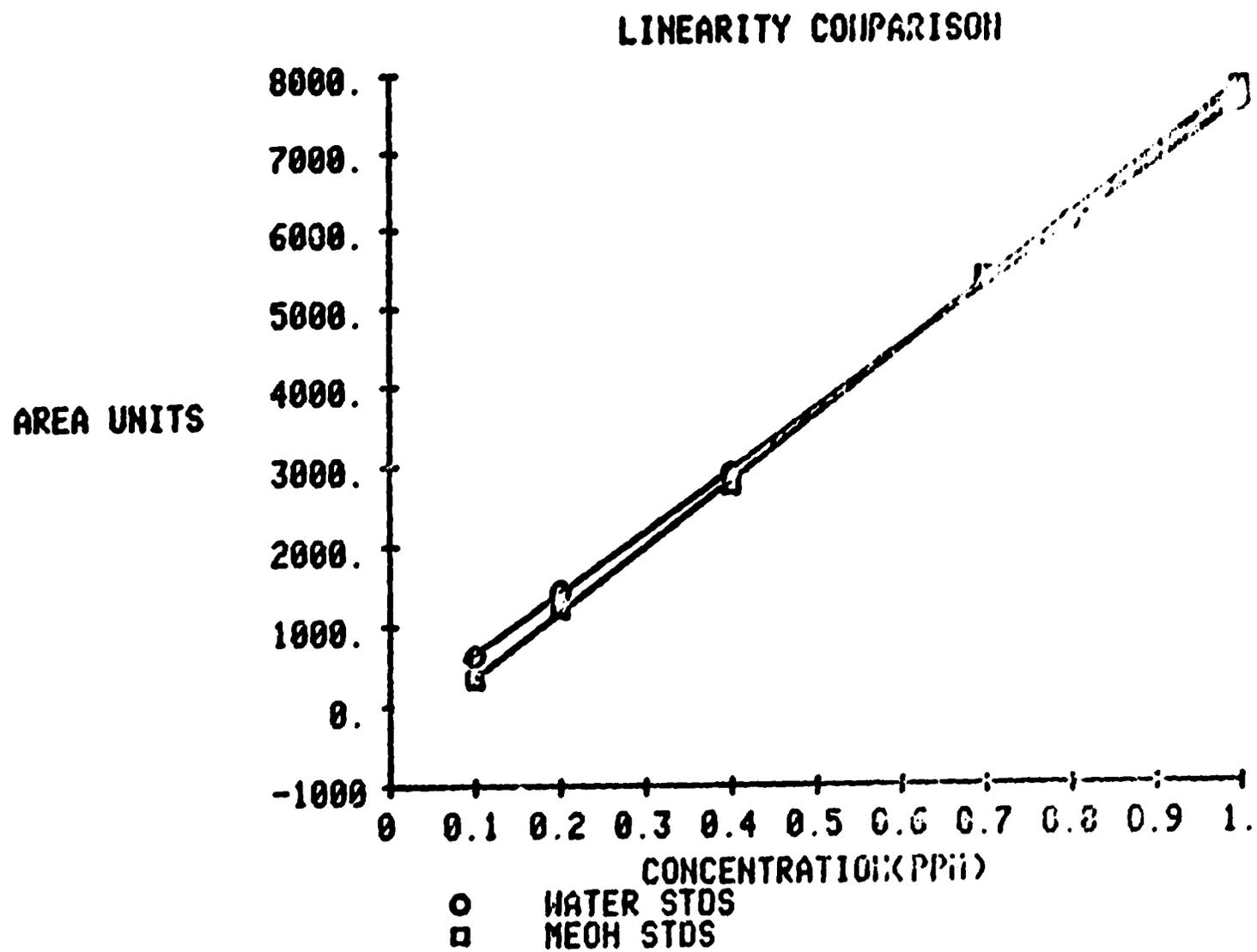
**FIGURE 3.** Effect of Solvent Matrix of 3,4-DCA



\*Data extrapolated from samples analyzed at an attenuation factor of 2 less sensitive than the attenuation used to generate the MeOH STDS values.

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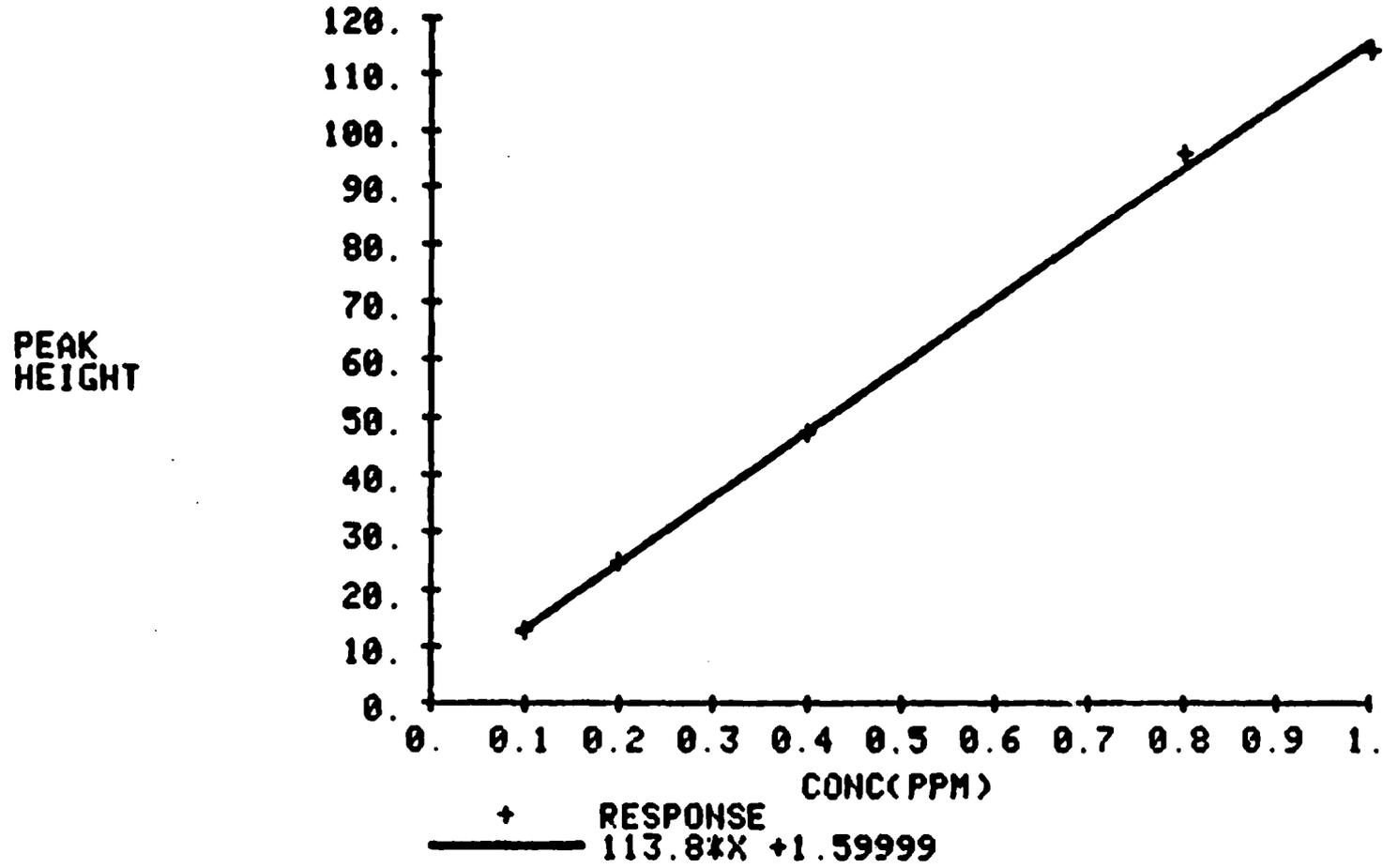
**FIGURE 4.** Effect of Solvent Matrix of 3,4-DCA



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FIGURE 5

LINEARITY/RESPONSE OF 3,4-DCA IN H<sub>2</sub>O



**FIGURE 6.** Comparison of UV Baseline During 2-Pump Isocratic Eluent Delivery and Single Pump Delivery on Hewlett Packard 1084B HPLC

**Conditions**

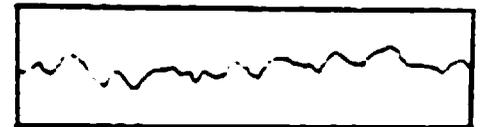
Flow: 1.5 mL/min  
Column: Zorbax® ODS  
Detection: UV @ 240 nm  
Eluent: 82% MeOH/18% Water  
Attn: 2<sup>5</sup>

Pump A → Water

Pump B → MeOH

Programmed to Deliver 82% from Pump B

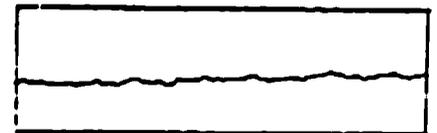
UV BASELINE



Pump B → 82% MeOH/18% Water

Programmed to Deliver 100% from Pump B

UV BASELINE



**TABLE 1A**

Replicate Injections  
of Water Standards  
of 3,4-DCA,  
Measurement by  
Peak Height

	1 1/29/81 AFTERNOON	2 1/29/81 EVENING	3 1/30/81 MORNING	4 1/30/81 AFTERNOON	Average
1.				12.5	12.5 mm ± 0%*
2. 0.1 PPM				12.5	
3.				12.5	
4.			25		24.5 mm ± 4%
5. 0.2 PPM			24		
6.			24.5		
7.	47	46	47		46.5 mm ± 3%
8. 0.4 PPM	47	46	46.5		
9.	47	45	47		
10.	97	94	95	95.5	95.5 mm ± 2%
11. 0.8 OLD	97	95	94	96	
12.	96	94	96	96	
13.				94	94.3 mm ± 1%
14. 0.8 NEW				94	
15.				95	
16.			113.5		113.5 mm ± 1%
17. 1.0 PPM			114		
18.			113		

**TABLE 1R**

Replicate Injections  
of Water Standards  
of 3,4-DCA,  
Measurement by  
Peak Area

	1 1/29/81 AFTERNOON	2 1/29/81 EVENING	3 1/30/81 MORNING	4 1/30/81 AFTERNOON	Average
1.				614	616 ± 16%*
2. 0.1 PPM				568	
3.				667	
4.			1455		1418 ± 5%
5. 0.2 PPM			1386		
6.			1413		
7.	2902	2870	2981		2889 ± 4%
8. 0.4 PPM	2927	2921	2775		
9.	2832	2888	2903		
10.	6300	6249	6245	6123	6238 ± 2%
11. 0.8 OLD	6272	6270	6202	6272	
12.	6269	6217	6233	6199	
13.				5994	6057 ± 2%
14. 0.8 NEW				6126	
15.				6050	
16.			7396		7591 ± 5%
17. 1.0 PPM			7560		
18.			7716		

\*Relative percent of average for all values in the 3 bracketed rows,  
2 S.D.

**TABLE 2.** Results of 3 Replicate Analyses of Hydrolysis and Photolysis Samples from 3,4-DCA Photolysis (Results in terms of peak height of 3,4-DCA peak, in mm)

	1 SAMPLE A	2 SAMPLE B
1.	95.	
2. 0 HR HYDRO†	95.	
3.	95.	
4.	94.	
5. 2 HR HYDRO†	93.	
6.	92.	
7.	80.	79.
8. 0.25 HR*	80.	79.
9.	60.5	78.5
10.	64.	64.
11. 0.5 HR*	64.	63.5
12.	64.	63.
13.	53.	51.
14. 0.75 HR*	52.5	51.
15.	52.5	51.
16.	42.5	43.
17. 1.0 HR*	42.	42.5
18.	42.	42.5
19.	30.	28.
20. 1.5 HR*	28.	27.
21.	30.	28.
22.	20.5	20.
23. 2.0 HR*	21.	20.5
24.	21.	20.

†Hydrolysis samples

\*Photolysis samples

TABLE 3. Amount of 3,4-DCA in Hydrolysis and Photolysis Samples from Photolysis Study on 1/29/81

	1 SAMPLE A PK HT	2 SAMPLE B PK HT	3 AVERAGE PK HT	4 CONC (PPM)
1. 0 HR HYDRO	95.		95.	0.834798
2. 2 HR HYDRO	93.		93.	0.817223
3. 0.25 HR PHOTO	80.2	78.8	79.5	0.698594
4. 0.5 HR PHOTO	64.	63.5	63.75	0.560193
5. 0.75 HR PHOTO	52.7	51.	51.85	0.455624
6. 1.0 HR PHOTO	42.2	42.7	42.45	0.373023
7. 1.5 HR PHOTO	29.3	27.7	28.5	0.250439
8. 2.0 HR PHOTO	20.8	20.2	20.5	0.180141

TITLE OF STUDY: The Determination of 3,4-Dichloroaniline (3,4-DCA) in Water by High Performance Liquid Chromatography (HPLC)

In compliance with Good Laboratory Practice Regulations, this study was inspected by the Quality Assurance Unit, and the results of these inspections reported to Management and the Study Director on the dates listed below. The report accurately reflects the data generated in accordance with the regulations and standard operating procedures of the Laboratory. All data and the reports are located at the submitting laboratory.

Study Started: 1/26/81

Report Issued Date: 4/24/81

Dates of Inspection: 4/20/81

Date of Report: 4/24/81

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W. M. McCarty 4/24/81  
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W. M. McCarty (Date)  
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Environmental Sciences Research  
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Dow Chemical U.S.A.  
Midland, MI 48640

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Contractor				21
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Doc Title	TOXICOLOGICAL PROPERTIES AND INDUSTRIAL HANDLING HAZARDS OF N,N-BIS(2,3-EPOXY-PROPYL)ANILINE			23
Chemical Name (300 per name)	25		CAS No. (10)	24
ANILINES			999999994	
N,N-BIS(2,3-EPOXY-PROPYL)ANILINE			2095-06-9	

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Biochemical Research Laboratory  
The Dow Chemical Company

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CENTRAL RESEARCH INDEX

TOXICOLOGICAL PROPERTIES AND INDUSTRIAL  
HANDLING HAZARDS OF N, N-BIS (2,3-EPOXY-  
PROPYL) ANILINE

File  
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Source Western Division  
Sub. By P. D. Aze  
Rept. By J. M. Morris

Signed J. M. Morris 12.20.68

Checked J. M. Morris 11.20.68

NOT A C  
JH

PROBLEM

A sample of N, N-bis (2,3-epoxypropyl) aniline was submitted to the Biochemical Research Laboratory for toxicological evaluation and definition of industrial handling hazards.

RESTRICTED: for use within The Dow Chemical Company only.

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CONCLUSIONS

The test material has a low acute oral toxicity and should present no problem of lethality from ingestion incidental to industrial handling.

Upon direct contact with the rabbit eye, the test material produced slight pain but essentially no conjunctival irritation or corneal injury. The test material would likely be no more irritating in the case of human eye exposure. Minimal eye protection is recommended for industrial handling whenever the likelihood of eye contact exists.

Results of laboratory tests conducted on rabbits, indicate that the test material is moderately irritating to intact and freshly abraded skin. Prolonged contact under conditions of confinement as exemplified by contaminated shoes, clothing and gloves, would likely result in slight blistering and burn. Repeated, prolonged exposure to unconfined skin, would likely result in a slight to moderate blistering and a slight to moderate burn.

Results of percutaneous absorption studies indicate that the test material is not absorbed through intact rabbit skin in acutely lethal amounts. Repeated exposure may present a problem.

Aniline and some derivatives of aniline are known to produce methemoglobinemia. The formation of methemoglobin as a result of exposure to N,N-bis (2,3-epoxypropyl) aniline was not determined in the present study. If interest develops in the test material further testing is indicated.

On the basis of the chemical structure of the test material and the known skin sensitizing property of similar compounds, this material should be handled as a potential skin and respiratory tract sensitizer.

Skin contact with the test material should be avoided, and protective clothing must be worn whenever the likelihood of such contact exists.

A comparison of the toxicological properties of N,N-bis (2,3-epoxypropyl) aniline and DFR 331 was requested. Range finding studies conducted on these materials indicate that both materials are essentially non-irritating to the eye. The ALD<sub>50</sub> of DFR 331 is

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greater than 2 g/kg body weight and the ALD<sub>50</sub> of N,N-bis (2,3-epoxy-propyl) aniline lies between 1 g/kg and 2 g/kg body weight. DER 331 is at the most only mildly irritating to the skin whereas N,N-bis (2,3-epoxypropyl) aniline is moderately irritating and, dependent upon the extent of the exposure, capable of causing a burn. DER 331 is a known sensitizer. On the basis of the similarity of chemical structure of N,N-bis (2,3-epoxy-propyl) aniline and until skin sensitization studies prove otherwise, N,N-bis (2,3-epoxypropyl) aniline should be handled as a skin sensitizer.

Our knowledge of the hazards involved with inhalation of vapors or fumes of aniline and substituent derivatives of aniline, would indicate that single exposure to the vapors or fumes of the test material may be a problem. If interest in the test material develops, inhalation studies are recommended to ascertain the degree of hazard involved in the industrial handling of the material.

The results of the range finding toxicological studies are intended for use as a guide in evaluating hazards from acute exposure, primarily for recommending precautions for safe industrial handling.

For the purpose of this study, the submitted sample was considered to be representative of the material that may be manufactured and used. Any change in manufacturing processes, batch size, raw materials or other variations which could result in an altered material, as well as the development of specific uses, for the concentrated material or formulation, may require additional studies, including the effects of repeated exposure, to re-define toxicological hazards.

SUMMARY OF TOXICOLOGICAL DATA

Acute Oral Toxicity

<u>Animal</u>	<u>Preparation Fed</u>	<u>Dose (g/kg)</u>	<u>No. Died/No. Fed</u>
Rat (M)	10% solution in corn oil	.126	0/2
		.252	0/2
		.50	0/2
		1.0	0/2
		2.0	2/2

Eye Contact - Rabbit

<u>Material</u>	<u>Treatment</u>	<u>Response-Remarks</u>
Undiluted	Washed and Unwashed	Slight pain on instillation. Eye essentially normal 24 hours post-instillation.

Skin Contact - Rabbit (Repeated Application)

<u>Material</u>	<u>Condition Of Skin</u>	<u>No. Of A-pl.</u>	<u>Site</u>	<u>Response-Remarks</u>
Undiluted	Intact	5	Ear	Slight hyperemia after the 1st application. Hyperemia increased to moderate after the 2nd application and persisted as such throughout the test period. Slight edema after the 3rd application persisted as such until the beginning of the 2nd week at which time it increased to moderate persisting as such until the end of the 1st day of the 2nd week, at which time applications were stopped. Necrotic area healed with a slight scab formation. Slight exfoliation and slight to moderate hair loss noted during the 2nd week and at the end of the 3rd week of test.

Biochemical Research Laboratory  
Page 3

Skin Contact - Rabbit (Repeated Application) - Continued

<u>Material</u>	<u>Condition Of Skin</u>	<u>No. Of Appl.</u>	<u>Site</u>	<u>Response-Remarks</u>
	Intact	2	Belly	Moderate hyperemia, slight edema and slight necrosis after the 1st application. Necrosis moderate after the 2nd application at which time applications were stopped. Hyperemia persisted as moderate for the 1st week, edema increased to moderate after the 2nd application subsided to slight for the remainder of the 1st week. Exposure site essentially free of hyperemia and edema during the 2nd week of test. Necrotic area healed with a slight scab and slight scar formation. Slight exfoliation observed during the 2nd and at the end of the 3rd week of test.
	Abraded	2	Belly	Response same as for intact belly skin except moderate scab and scar formation resulted.
10% solution in Dowanol DPN	Intact	10	Ear	Slight hyperemia after the 1st 3 applications. Hyperemia increased to moderate after the 4th and subsided to slight by the 1st of the 2nd week of test and persisted as such throughout the entire test period. Slight exfoliation observed at the end of the 1st week of test, persisted as such throughout the entire test period.

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Skin Contact - Rabbit (Repeated Application) - Continued

<u>Material</u>	<u>Condition Of Skin</u>	<u>No. Of Appl.</u>	<u>Site</u>	<u>Response-Remarks</u>
10% solution in Dowanol DPM	Intact	10	Belly	Slight hyperemia observed after the 2nd application increased to moderate after the 4th application and per- sisted as such until the end of the 2nd week of test at which time it subsided to slight. Slight to moderate exfoliation observed during the 2nd week of test.
	Abraded	3	Belly	Slight hyperemia after the 1st application. Hyperemia increased to moderate after the 2nd and 3rd application and persisted as such for 1 more day. Exposure site essentially free of hyperemia during the 2nd week of test. Slight edema after the 2nd application persisted as such for the remainder of the 1st week of test. Slight exfol- iation observed during the 2nd week of test.

Skin Absorption

There is no indication, from the skin irritation tests conducted, that the undiluted test material is absorbed through the skin in acutely toxic amounts. However the test material, as a 10% solution in Dowanol DPM, caused persistent weight loss in the animals under test and would indicate that the material was being absorbed through the skin in toxic amounts.

**FIRST AID MEASURES**

<p><b>EYE CONTACT</b></p>	<p><input checked="" type="checkbox"/> If the eyes are contaminated, they should be flushed immediately with copious amounts of flowing water for at least 15 minutes.</p> <p><input type="checkbox"/> ...</p> <p><input type="checkbox"/> ...</p> <p><b>ADDITIONAL ATTENTION SHOULD BE OBTAINED IMMEDIATELY AS NECESSARY.</b></p>
<p><b>SKIN CONTACT</b></p>	<p><input checked="" type="checkbox"/> Any contact of substances which may develop should remove affected persons.</p> <p><input type="checkbox"/> Contaminated clothing and shoes should be removed and the person should be thoroughly cleaned.</p> <p><input type="checkbox"/> Wash contaminated skin with soap and plenty of water.</p> <p><input type="checkbox"/> Contaminated clothing, including shoes, should be removed and the affected skin areas should be washed thoroughly with soap and plenty of water.</p> <p><input type="checkbox"/> Unaffected skin should also be washed.</p> <p><input type="checkbox"/> Contaminated clothing and shoes should be removed and thoroughly cleaned.</p> <p><input checked="" type="checkbox"/> All contaminated clothing, including shoes, should be removed immediately and the affected skin areas flushed thoroughly with water from a shower cabinet, or other suitable device and flushed with soap and plenty of water.</p> <p><input type="checkbox"/> <b>ADDITIONAL ATTENTION SHOULD BE OBTAINED IMMEDIATELY AS NECESSARY.</b></p> <p><input checked="" type="checkbox"/> Contaminated clothing including shoes, must be removed and thoroughly cleaned or must be discarded.</p>
<p><b>INHALATION</b></p>	<p><input type="checkbox"/> If a person should experience any respiratory distress from breathing the vapor or fumes of this material, medical attention should be obtained promptly.</p> <p><input type="checkbox"/> If a person should experience any respiratory distress from breathing the material, he should be removed to fresh air as soon as possible, and <b>MEDICAL ATTENTION SHOULD BE OBTAINED IMMEDIATELY.</b> If breathing stops, artificial respiration should be administered.</p>
<p><b>INGESTION</b></p>	<p><input type="checkbox"/> If appreciable amounts of material are swallowed, vomiting should be induced by rubbing the back of the tongue with the finger or by giving an emetic such as 1 tablespoonful of table salt in a glass of warm water. Medical attention should also be obtained.</p> <p><input type="checkbox"/> If the material is swallowed, vomiting should be induced by rubbing the back of the tongue with the finger or by giving an emetic such as 1 tablespoonful of table salt in a glass of warm water. <b>ADDITIONAL ATTENTION SHOULD BE OBTAINED IMMEDIATELY AS NECESSARY.</b></p>

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CATEGORIES OF DEFENSES RELATED TO TYPES OF OPERATIONS	PRACTICES AND DEFENSES				
	TYPE	DEFENSE	DEFENSE	DEFENSE	DEFENSE
1. DEFENSES OF GENERAL APPLICATION WITH REGARD TO THE USE OF DEFENSES					
2. DEFENSES OF GENERAL APPLICATION WITH REGARD TO THE USE OF DEFENSES					
3. DEFENSES OF GENERAL APPLICATION WITH REGARD TO THE USE OF DEFENSES					
4. DEFENSES OF GENERAL APPLICATION WITH REGARD TO THE USE OF DEFENSES					
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10. DEFENSES OF GENERAL APPLICATION WITH REGARD TO THE USE OF DEFENSES					

Comments: "GOOD PRACTICE DEFENSES" THAT  
 DEFENSES OF ANY CHARACTER  
 BE DEFENSES OF THE TYPE AS  
 SHOWN AS PRACTICAL

"BUTABLE GAS MASK CARTRIDGE"  
**Organic Vapor**

Name J. M. Morris . T. R. Torkelson M. R. Hoyle  
 Date 11/21/68 12/6/68

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