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**EDGEWOOD ARSENAL
TECHNICAL REPORT**

EATR 4439

**TOXICOLOGICAL STUDIES ON
THE HERBICIDE "WHITE" IN ANIMALS**

by

J. T. Weimer

T. A. Ballard

E. J. Owens

B. P. McNamara, Ph. D.

September 1970



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**DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Research Laboratories
Medical Research Laboratory
Edgewood Arsenal, Maryland 21010**

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Toxicology Department

September 1970

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Task 1B662710AD6201

**DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Research Laboratories
Medical Research Laboratory
Edgewood Arsenal, Maryland 21010**

FOREWORD

The work described in this report was authorized under Task 1B662710AD6201, Simulant and Training Agent Investigations, Biomedical Evaluation of Simulant and Training Agents (U). The work was started in June and completed in September 1967.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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DIGEST

WHITE is a herbicide used extensively as a defoliant and weed killer. The purpose of this study was to assess the biological effects of this system in animals under conditions of moderate and high temperature and humidity.

Toxicological studies indicate that a single, direct exposure to a spray of **WHITE** would not be likely to constitute a hazard to the skin nor a systemic hazard by inhalation. Contamination of the eyes by droplets as large as 0.2 ml would not be expected to produce permanent damage. Temporary irritation and corneal opacity could result from droplets of 0.05 to 0.2 ml.

Repeated exposures of the same skin area could result in local cutaneous damage that would be reversible when exposures were discontinued.

Based on intragastric and oral toxicity studies in several animal species, a man would have to swallow grams-per-kilogram quantities of **WHITE** for a single dose to be lethal.

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CONTENTS

	Page
I. INTRODUCTION	7
A. Acute Oral Toxicity of Single Doses	7
B. Repeated Oral Doses in Sheep	8
C. Chronic Oral Toxicity of TORDON in Dogs and Rats	8
D. Single Doses on the Skin of Rabbits	9
E. Repeated Doses on the Skin of Rabbits and Men	9
F. Application to the Eyes of Rabbits	9
G. Vapor Inhalation in Rats	9
II. STUDIES CONDUCTED AT EDGEWOOD ARSENAL RESEARCH LABORATORIES	9
A. Materials and Methods	9
B. Results	12
C. Inhalation Toxicity in Rabbits and Rats	13
III. SUMMARY AND CONCLUSIONS	13
DISTRIBUTION LIST	27

LIST OF TABLES

Table	Page
I Cutaneous Effects of Single Doses of WHITE in Clipped Rabbits at Moderate Temperatures and Humidities	14
II Cutaneous Effects of Single Doses of WHITE in Clipped Rabbits at High Temperatures and Humidities	15
III Cutaneous Effects of Five Daily Doses of WHITE in Clipped Rabbits at Moderate Temperatures and Humidities	16
IV Cutaneous Effects of Five Daily Doses of WHITE in Clipped Rabbits at High Temperatures and Humidities	17
V Cutaneous Effects of Single Doses of WHITE Through Two Layers of Clothing (T-Shirt and Sateen) in Clipped Rabbits	18
VI Cutaneous Effects of Five Daily Doses of WHITE Through Two Layers of Clothing (T-shirt and Sateen) at Moderate Temperatures and Relative Humidities in Clipped Rabbits	19
VII Ocular Effects of Single Doses of WHITE in Untreated Rabbits at Moderate Temperatures and Humidities	21
VIII Ocular Effects of Single Doses of WHITE in Rabbits (Treated Daily With Antibiotics) at Moderate Temperatures and Humidities	23
IX Ocular Effects of Single Doses of WHITE in Rabbits (Treated Daily With Antibiotics) at High Temperatures and Humidities	24
X Intragastric (Stomach Tube) Toxicity of WHITE in Rabbits	25
XI Intragastric (Stomach Tube) Toxicity of WHITE in Rats	25
XII Toxicity of WHITE in Rats and Rabbits Following a Single Inhalation Exposure	26
XIII Bliss Regression Line for Inhalation Toxicity of WHITE in Rabbits	26

TOXICOLOGICAL STUDIES ON THE HERBICIDE "WHITE" IN ANIMALS

I. INTRODUCTION.

WHITE is a herbicide that may be used over wide areas. The purpose of this study was to assess the biological effects of this material in animals under conditions of moderate and high temperatures and humidities.

WHITE is the military designation for TORDON 101 Mixture.* TORDON is the registered trademark for 4-amino-3,5,6-trichloropicolinic acid and its potassium and triisopropanolamine salt formulations. TORDON 101 Mixture contains the following:

10.2% triisopropanolamine salt of 4-amino-3,5,6-trichloropicolinic acid
39.6% triisopropanolamine salt of 2,4-dichlorophenoxyacetate (2,4-D)

The remaining 50.2% is not identified by Dow Chemical Company other than as water and a surfactant. According to information supplied by the manufacturer, the proportions of the ingredients may vary slightly from batch to batch. The specific gravity of WHITE is 1.135.

The toxicological studies of WHITE previously reported** are as follows.

A. Acute Oral Toxicity of Single Doses.

<u>Species</u>	<u>Dose of WHITE</u> <i>mg/kg</i>	<u>Effect</u>
Rat	3080	LD50
Sheep	1265	No ill effect
	1900	No ill effect
	2200	Dead in 3 days
	5000	3/3 dead in 1 day
Cattle	1265	No ill effect
	1900	Toxic signs followed by recovery.
	2530	Toxic signs followed by recovery.
	3163	Toxic signs followed by recovery.

*Dow Chemical Company, Midlands, Michigan.

**Lynn, G. E. A Review of Toxicology Information on TORDON Herbicides. Down to Earth (a Dow Chemical Co. publication) 20, 6-8 (1965). In some instances, the cited publication does not give all the details of the experiments.

B. Repeated Oral Doses in Sheep.

<u>Number of sheep</u>	<u>Daily dose of WHITE</u> <u>ml/kg</u>	<u>Results</u>
11	0.55	One died on the fifth day of feeding; 1 died 10 days, 1 died 11 days, and 2 died 10 days after 5 days of feeding.
11	0.11	No adverse effect on weight gain; no deaths in 30 days of feeding.

C. Chronic Oral Toxicity of TORDON in Dogs and Rats.

The 4-amino-3,5,6-trichloropicolinic acid component of WHITE was fed to beagles* and rats** in daily doses of 15, 50, and 150 mg/kg for 2 years. The study in dogs revealed no adverse effects on the following:

- Body weight
- Food consumption
- Survival
- Behavioral patterns
- Blood chemistry
- Urine
- Liver function
- Physical fitness
- Organs, gross and microscopic characteristics
- Body weight and organ/weight ratios

The study in rats revealed no formation of tumors and no adverse effects on the following:

- Survival
- Growth
- Food consumption and utilization
- Urine
- Blood chemistry
- Organs, gross and microscopic characteristics
- Body weight and organ/weight ratios

*Beagles - Two-year chronic oral toxicity of TORDON Beagle Dogs. Dow Chemical Company. 27 June 1965.

**Rats - Chronic oral toxicity of TORDON Albino Rats. Dow Chemical Company. 21 October 1965.

D. Single Doses on the Skin of Rabbits.

Two grams of WHITE per kilogram of body weight, applied under an impervious cuff to the clipped dorsal skin of rabbits for 24 hours caused slight hyperemia and slight necrosis. Otherwise, the animals appeared normal during and after exposure.

E. Repeated Doses on the Skin of Rabbits and Men.

1. Rabbits.

Prolonged contact of undiluted WHITE with rabbits' ears resulted in slight irritation. Exposures of abraded and intact areas of skin of the belly and occlusion with a bandage resulted in slight irritation and some swelling. Repeated, prolonged, confined contact resulted in scabs. The intact and abraded skin areas returned to normal following cessation of application.

Fifteen milliliters of a 5% solution of WHITE in water was applied 5 days/week for 3 weeks to about 30 sq in. of intact and abraded rabbit skin. The solution was kept in contact with the skin for 7 hours/day by application to a cloth pad under a plastic wrapping. At the end of each exposure period, the area was washed. There were no signs of skin irritation or interference with healing of abrasions. All animals appeared normal and none died. Microscopic examination of various tissues showed no effects attributable to WHITE.

2. Man.

Repeat-and-challenge applications of a 5% solution of WHITE in water produced no skin irritation or skin sensitization.

F. Application to the Eyes of Rabbits.

WHITE, applied directly to the eyes of rabbits, produced some conjunctival redness and slight swelling, accompanied by transient corneal injury. The irritation and injury subsided in 1 week.

G. Vapor Inhalation in Rats.

There were no adverse effects in rats exposed for 7 hours to an atmosphere produced by bubbling air through WHITE.

II. STUDIES CONDUCTED AT EDGEWOOD ARSENAL RESEARCH LABORATORIES.

A. Materials and Methods.

1. Materials.

A "standard" of WHITE, obtained from the manufacturer, was similar to the commercial product except that it contained exact quantities of analytical grade TORDON and 2,4-D. (The commercial product contains technical grade materials.) The standard contained the following.

	<u>Based on acid form</u>	<u>Based on trisopropanolamine salt</u>
		%
LORDON	6.5	11.7
2,4-D	24.0	44.9

The remaining constituents of the standard were not divulged by the manufacturer, but the major portion presumably was water. The total active ingredients were assayed chemically by relating ultraviolet absorption of the standard and unknown preparations at a wavelength of 222 mμ.

Two samples of WHITE, obtained from Fort Detrick, were used in the toxicity studies conducted in this laboratory. Ultraviolet assay showed that both of the Fort Detrick samples and the manufacturer's standard were identical, and all three preparations were as potent as commercial WHITE.

2. Methods.

a. Bare Skin of Rabbits.

The various bare skin tests in rabbits were as follows:

- (1) Local effects of single doses under temperate conditions (69° to 88°F; 58% to 88% RH).*
- (2) Local effects of single doses under tropical conditions (92° to 95°F; 93% to 99% RH).
- (3) Local effects of doses applied on five successive days under temperate conditions (64° to 90°F; 46% to 79% RH).
- (4) Local effects of doses applied on five successive days under tropical conditions (92° to 93°F; 93% to 99% RH).

The backs of albino rabbits were clipped the day before WHITE was applied. The undiluted liquid was dispensed from 0.25- to 0.5-ml syringes for doses greater than 0.1 ml. Smaller doses were dispensed from a Hamilton microliter syringe. The doses were applied only to undamaged skin areas. The area of application was examined twice daily for 30 days.

All rabbits were kept in individual cages. For studies under temperate conditions, the animals were housed in the animal-holding facility. For studies at elevated temperatures and humidities, the animals were housed in the climatic facility under controlled environmental conditions continuously from 2 weeks before exposure until observations were completed after exposure. Many control and test rabbits at the high temperatures and humidities died before and after WHITE was applied.

*Variation reflects seasonal changes in the temperature of the animal-holding facilities.

b. Clothed Skin of Rabbits.

The various tests on clothed skin were as follows: (1) Local effects of single doses. Ambient conditions were 77° to 88°F and 57% to 65% RH. (2) Local effects of doses applied on 5 successive days. Ambient conditions were 72° to 84°F and 48% to 87% RH.

The rabbits were clipped and handled as in the bare skin studies. Cotton T-shirt material covered by sateen was taped over the bare, undamaged skin 30 minutes before WHITE was applied. The liquid was placed on the outer layer of sateen, and the contaminated clothing remained in place for 48 hours. Following this, the skin was examined twice daily for 30 days. Many of the control and test animals succumbed to the climatic conditions when elevated temperatures and humidities were used.

c. Eyes of Rabbits.

The various tests performed on the eyes of rabbits were as follows: (1) Local effects of single doses under moderate conditions of temperature and relative humidity. No measures to prevent infection were taken. (2) Local effects of single doses under moderate conditions of temperature and humidity. The eyes were treated daily. (3) Local effects of single doses under tropical conditions (92° to 95°F; temperature 93% to 99% RH). The eyes were treated daily.

Rabbits were housed at moderate or elevated temperatures and humidities, as explained above. The undiluted WHITE was applied to one eye from a Hamilton microliter syringe. The other eye served as a control. All eyes were examined twice each day for 30 days following application. Some groups of rabbits were given no treatment. The eyes of other groups were cleansed of exudates and irrigated daily with water, and a 15% ophthalmic solution of sodium sulfacetamide (Alcon Lab., Fort Worth, Texas) was applied once daily to prevent infection. Many control and test animals died at the high temperatures and humidities before and after WHITE was applied.

d. Intragastric Toxicity in Rabbits and Rats.

Undiluted WHITE was administered to rats and rabbits by stomach tube, and the LD50 values that cause death within 48 hours and within 5 days, respectively, were calculated by the method of Bliss.*

e. Inhalation Toxicity in Rabbits and Rats.

The inhalation toxicity of 1 μ aerosol particles of WHITE was determined by simultaneous total-body exposure of 10 individually caged rats and 6 uncaged rabbits. Four volumes of WHITE were diluted with six volumes of water and dispersed in a chamber. The airborne sample of 2,4-D plus TORDON was collected using glass-fiber filter discs and vapor bubblers in series. The samples were analyzed on an ultraviolet spectrophotometer at 222 m μ .

*Bliss, C. I. The Statistics of Bioassay. Academic Press, Inc., New York, 1952.

B. Results.

1. Bare Skin of Rabbits.

Single doses of 0.03, 0.05, 0.10, and 0.50 ml of WHITE produced nothing more serious than erythema when applied to the bare skin of rabbits under moderate or elevated temperature and humidity. The skin of all animals appeared normal within 4 days (tables I and II).*

By the time of the fifth daily dose of 0.001, 0.02, 0.03, 0.10, or 0.50 ml at moderate temperatures and humidities, only erythema had appeared. Three days after the fifth dose, most of the rabbits had necrotic areas. Except for one rabbit at the highest dose, all necrotic areas had healed within 6 days after the last dose (table III).

When temperature and humidity were elevated and 0.02 ml of WHITE was applied to the bare skin of rabbits, the first dose produced erythema, and necrosis occurred after the third dose. Some of this damage remained as long as 10 days. Many control and test animals succumbed to the climatic conditions and the experiment was terminated (table IV).

2. Clothed Skin of Rabbits.

Single doses of 0.001, 0.02, 0.03, 0.10, and 0.50 ml applied to sateen over cotton T-shirt material worn for 48 hours at moderate conditions of temperature and humidity produced only erythema, which disappeared 3 days later (table V).

When WHITE was applied in five daily doses of 0.001, 0.02, 0.03, 0.10, and 0.50 ml to the same clothing assembly under moderate conditions of temperature and humidity, the three lowest doses produced no noticeable effects (table VI). The dose of 0.10 ml produced only erythema, which disappeared by the fourth day after the last application. After the fifth dose of 0.50 ml, erythema was seen in all animals and one rabbit had necrosis. The erythema had disappeared by the ninth postexposure day, and the necrotic area appeared normal on the 11th postexposure day.

3. Eyes.

Under conditions of moderate temperature and humidity and no treatment, single doses of 0.005 ml had no effect and 0.01 ml caused some blepharitis, iritis, and conjunctivitis, which disappeared in 10 days (table VII). Doses of 0.05, 0.10, and 0.2 ml produced the previously mentioned signs plus corneal opacity in both treated and untreated eyes. The corneal opacity disappeared in 21 and 28 days in treated and untreated eyes, respectively (table VIII).

The eyes of the rabbits tested at elevated temperatures and humidities were treated daily with antibiotic. Single doses of 0.005 ml produced no ocular effects (table IX). Doses of 0.01 ml caused blepharitis which disappeared within 1 week. Some blepharitis was still noticeable 10 days after exposure to 0.05 ml. The experiment was terminated at 10 days because the climatic conditions were killing the rabbits. The local ocular damage was similar to that seen under temperate conditions.

*Tables I through XIII may be found at the end of the text.

4. Intragastric Toxicity in Rabbits and Rats.

The LD50 for undiluted WHITE administered to rabbits by stomach tube was 1.67 (1.02 to 2.71) ml/kg for a 5-day observation period (table X). The animals became inactive but exhibited no other signs of toxicity before dying. All deaths occurred within 24 hours. Survivors appeared normal within 24 hours.

The LD50 for undiluted WHITE administered by stomach tube to rats was 4.17 (3.02 to 5.76) ml/kg for a 48-hour observation period (table XI). These animals became inactive, but showed no other signs of toxicity before dying. All deaths occurred within 24 to 30 hours. Surviving rats appeared normal within 24 hours.

C. Inhalation Toxicity in Rabbits and Rats.

The inhalation LC150 for a single exposure to aerosols of WHITE in rabbits is 150,982 (79,358 to 287,252) mg-min/cu m (tables XII and XIII). The animals kept their eyes closed and became inactive during exposure, but their respiration appeared normal. Immediately after exposure, there were no signs of ocular or nasal irritation. Four to 5 days after exposure, mild to moderate blepharitis was noted. The eyes were partially closed and the lids were erythematous. The eyes were normal 8 days after exposure. Two rabbits died within 24 hours after exposure. Four others died on the fifth, sixth, ninth, and 14th days, respectively.

The rats kept their eyes closed and became inactive during the exposure. There were no postexposure signs and no deaths.

III. SUMMARY AND CONCLUSIONS.

The toxicological studies performed indicate that a single, direct exposure to a spray of WHITE would probably not constitute a hazard to the skin nor a systemic hazard by inhalation. Contamination of the eyes by droplets as large as 0.2 ml would not be expected to produce permanent damage. Temporary irritation and corneal opacity could result from droplets of 0.05 to 0.2 ml.

Repeated exposures of the same skin area could result in local cutaneous damage which would be reversible when exposures were discontinued.

Based on intragastric and oral toxicity studies in several animal species, a man would have to swallow grams-per-kilogram quantities of WHITE for a single dose to be lethal.

Table 1. Cutaneous Effects of Single Doses of WHITE in Clipped Rabbits at Moderate Temperatures and Humidities

Rabbit No	Dose	Effects during postexposure period					
		1 Day	2 Days	3 Days	4 Days	6 Days	7 Days
		Temp (°F) 69 RH (%) 72	83 70	81 76		79 61	
	<i>ml</i>						
1	0.5	E-	E	R		R	
2	0.5	E	R	R		R	
3	0.5	E	R	R		R	
4	0.5	O	E	R		R	
5	0.5	E-	E	R		R	
6	0.5	E-	E-	R		R	
7	0.1	E-	E-	R		R	
8	0.1	O	O	O		O	
9	0.1	O	O	O		O	
10	0.1	O	O	O		O	
11	0.1	-	R	R		R	
12	0.1	O	O	O		O	
		Temp (°F) 79 RH (%) 88	88 65	85 60	76 58		82 60
13	0.03	E	R	R	R		R
14	0.03	E	E	R	R		R
15	0.03	E	E+	E	R		R
16	0.03	E	E	R	R		R
17	0.03	E	E	E	R		R
18	0.03	E	R	R	R		R

Legend for tables I to VI:

O = No effect

E- = Mild erythema

E = Moderate erythema

E+ = Severe erythema

N = Moderate necrosis

N+ = Severe necrosis

S = Swelling

R = Recovery

Table II Cutaneous Effects of Single Doses of WHITE in Chipped Rabbits
at High Temperatures and Humidities

Rabbit No.	Dose	Effect during postexposure period			
		1 Day	2 Days	3 Days	4 Days
		Temp (°F) 93 RH (%) 93	93 98	95 99	92 99
	<i>ml</i>				
1	0.5	E-	E-	R	R
2	0.5	E-	E-	R	R
3	0.5	E-	E	E-	R
4	0.5	E-	E-	R	R
5	0.1	E-	E	E	R
6	0.1	O	E-	R	R
7	0.1	E-	E	E	R
8	0.05	E-	E-	R	R
9	0.05	E-	E-	E-	R
10	0.05	O	O	O	O
11	0.05	E-	E-	R	R
12	0.05	E-	E-	E-	R
13	0.05	O	E-	R	R

NOTE: See legend, table I.

Table III. Cutaneous Effects of Five Daily Doses of WHITE in Clipped Rabbits at Moderate Temperatures and Humidities

Rabbit No	Daily dose	Effects during exposure and postexposure period								
		1 Day	2 Days	3 Days	4 Days	5 Days	8 Days	9 Days	10 Days	11 Days
		Temp (°F) RH (%)	64 68	68 62	72 46	73 53	90 64	74 78	79 57	78 68
	ml									
1	0.50	O	O	E	E	E+	N, E+	N, E+	E	E
2	0.50	O	O	E	E	E+	N, E+	N, E+	R	R
3	0.50	O	O	E	E	E+	N, E+	N, E+	N, E	E
4	0.50	O	O	E	E	E+	N, E+	N, E+	N, E+	E
5	0.50	O	O	E	E	E+	N, E+	N, E+	N, S	E, N
6	0.50	O	O	E	E	E+	N, E+	N, E+	E	E
7	0.10	O	O	E	E	E+	N	N	E	E
8	0.10	O	O	E	E	E+	N-	N, E	E	E
9	0.10	O	O	E	E	E+	N-	N-, E	R	R
10	0.10	O	O	E	E	E+	E+	E	R	R
11	0.10	O	O	E	E	E+	N-, E+	N-, E	E	E
12	0.10	O	O	E	E	E+	N-, E	E-	R	R
13	0.03	O	O	E	E	E+	N-, E+	E	R	R
14	0.03	O	O	E	E	E	E+	E	R	R
15	0.03	O	O	E	E	E+	N-, E	E	R	R
16	0.03	O	O	E	E	E	N-, E	E-	R	R
17	0.03	O	O	E	E	E	E	R	R	R
18	0.03	O	O	E	E	E	N-, E	R	R	R
19	0.02	O	O	E	E	E	E	R	R	R
20	0.02	O	O	E	E	E	N-	E	R	R
21*	0.02									
22	0.02	O	O	E	E	E	E	R	R	R
23	0.02	O	O	E	E	E	E	R	R	R
24	0.02	O	O	E	E	E	N-, E	E	E-	E

*Died, diarrhea apparent on first day.

Table III. Continued

Rabbit No.	Daily dose	Effects during exposure and postexposure period								
		1 Day	2 Days	3 Days	4 Days	5 Days	8 Days	9 Days	10 Days	11 Days
		Temp (°F) RH (%)	64 68	68 62	72 46	73 53	90 64	74 78	79 57	78 68
	ml									
25	0.001	O	O	E	E	E	E	R	R	R
26	0.001	O	O	E	E	E	N-	R	R	R
27	0.001	O	O	E	E	E	E	R	R	R
28	0.001	O	O	E	E	E	N, E	R	R	R
29	0.001	O	O	E	E	E	N-	R	R	R
30	0.001	O	O	E	E	E	N-	R	R	R

NOTE: See table I for legend.

Table IV. Cutaneous Effects of Five Daily Doses of WHITE in Clipped Rabbits at High Temperatures and Humidities

Rabbit No.	Daily dose	Effects during exposure and postexposure period						
		1 Day	2 Days	3 Days	4 Days	7 Days	10 Days	14 Days
		Temp (°F) RH (%)	93 93	93 98	95 99	92 99	93 98	95 99
	<i>ml</i>							
1	0.02	E-	E, S	N, S	N, S	N, S	N, S	Dead
2	0.02	E-	E	E	E-	R	R	R
3	0.02	O	E	E	E+	E-	R	Dead
4	0.02	E-	E	E+, S	E+, S, N	S, N	S, N	Dead
5	0.02	E-	E	E+, S, N	E+, S, N	E+, S, N	Sloughing	R
6	0.02	O	E	E+, S, N	E+, S, N	E, S, N	N	Dead

NOTE: See table I for legend.

Table V. Cutaneous Effects of Single Doses of WHITE Through Two Layers of Clothing (T-Shirt and Sateen)* in Clipped Rabbits

Rabbit No.	Dose	Effects during postexposure period				
		2 Days		3 Days	4 Days	5 Days
		Temp (°F)	88	85	76	77
		RH (%)	65	60	58	57
	<i>ml</i>					
1	0.50	E+	E	E	R	
2	0.50	E+	E+	E	R	
3	0.50	E	R	R	R	
4	0.50	E	E	R	R	
5	0.50	E+	E	R	R	
6	0.50	E	R	R	R	
7	0.10	O	E+	E-	R	
8	0.10	O	E+	E-	R	
9	0.10	O	E+	E-	R	
10	0.10	O	E+	E-	R	
11	0.10	O	O	O	O	
12	0.10	O	O	O	O	
13	0.03	O	O	O	O	
14	0.03	O	O	O	O	
15	0.03	O	O	O	O	
16	0.03	O	O	O	O	
17	0.03	O	O	O	O	
18	0.03	O	O	O	O	
19	0.02	O	O	O	O	
20	0.02	O	O	O	O	
21	0.02	O	O	O	O	
22	0.02	O	O	O	O	
23	0.02	O	O	O	O	
24	0.02	O	O	O	O	
25	0.001	O	O	O	O	
26	0.001	O	O	O	O	
27	0.001	O	O	O	O	
28	0.001	O	O	O	O	
29	0.001	O	O	O	O	
30	0.001	O	O	O	O	

*The contaminated clothing was removed after 48 hours.
NOTE: See table I for legend.

Table VI. Cutaneous Effects of Five Daily Doses* of WHITE Through Two Layers of Clothing (T-shirt and Sateen) at Moderate Temperatures and Relative Humidities in Clipped Rabbits

Rabbit No.	Dose	1 Day		Effects during postexposure period (following 5th dose)						
				3 Days	4 Days	5 Days	8 Days	9 Days	10 Days	11 Days
		Temp (°F)	77	75	73	73	74	72	74	73
		RH (%)	95	78	87	96	48	74	78	96
	<i>ml</i>									
1	0.50	E		R	R	R	R	R	R	R
2	0.50	N		N	N	N	E+	E+	F	R
3	0.50	E+		E	E	R	R	R	R	R
4	0.50	E+		E	E	E	R	R	R	R
5	0.50	E		R	R	R	R	R	R	R
6	0.50	E+		R	R	R	R	R	R	R
7	0.10	E		R	R	R	R	R	R	R
8	0.10	E		R	R	R	R	R	R	R
9	0.10	E		R	R	R	R	R	R	R
10	0.10	E		R	R	R	R	R	R	R
11	0.10	E		R	R	R	R	R	R	R
12	0.10	E		E	R	R	R	R	R	R
13	0.03	E		R	R	R	R	R	R	R
14	0.03	O								
15	0.03	O								
16	0.03	O								
17	0.03	O								
18	0.03	O								
19	0.02	O								
20	0.02	O								
21	0.02	O								
22	0.02	O								
23	0.02	O								
24	0.02	O								

*See footnote at end of table.

Table VI. Continued.

Rabbit No.	Dose	Effects during postexposure period (following 5th dose)							
		1 Day	3 Days	4 Days	5 Days	8 Days	9 Days	10 Days	11 Days
		Temp (°F) 77 RH (%) 95	75 78	73 87	73 96	74 48	72 74	74 78	73 96
	<i>mi</i>								
25	0.001	0							
26	0.001	0							
27	0.001	0							
28**	0.001								
29	0.001	0							
30	0.001	0							

*Temp and RH on days of dosing:

- 1 82°F 61%
- 2 82°F 62%
- 3 84°F 74%
- 4 83°F 77%
- 5 80°F 84%

**Died 4th day of dosing (appeared sick, had diarrhea prior to application).

NOTE: See table I for legend.

Table VII. Ocular Effects of Single Doses of WHITE in Untreated Rabbits at Moderate Temperatures and Humidities

Rabbit No.	Dose	Effects during postexposure period									
		1 Day	2 Days	3 Days	6 Days	8 Days	10 Days	13 Days	15 Days	21 Days	28 Days
		Temp (°F) RH (%)	69 72	83 70	81 76	79 61	82 60				
	ml										
1	0.2	B+, I+	B+, I+	B+, I+, CO	B+, I+, CO	B+, I+, CO	B, I, CO	B-, CO	B-, CO	CO	R
2	0.2	B+, I+, CO	B+, I+, CO	B+, I+, CO	B-, I+, CO-	C+, CO-	CO-	R	R	R	R
3	0.2	B+, I+	B+, I+	B+, I+	B+, I+, CO	B-, I+, CO	I, CO	CO	CO	CO-	R
4	0.2	B+, I+	B+, I+	B+, I+	B+, I+, CO, S	B+, I+, CO	B, I, CO	B, CO	B, CO	CO-	R
5	0.2	B+, I+	B+, I+	B+, I+	B+, I+, CO, S	B+, I+, CO	B, I, CO	B, CO	B, CO	CO-	R
6	0.2	B+, I+, CO	B+, I+, CO	B+, I+, CO	B+, I+, CO, S-	B+, I+, CO	B, I, CO	I, CO	I	R	R
7	0.1	B+, I	B+, I+, CO	B+, I+, CO	B+, I+, CO	B+, I+, CO	B, I, CO	CO	CO	CO	R
8	0.1	B+, I	B+, I+, CO	B+, I+, CO	B, I, CO	3- I, CO	B-, CO	R	R	R	R
9	0.1	B-, I-	B, I	B	C+, I, CO	C, CO	CO-	R	R	R	R
10	0.1	B+, I+	B+, I+	B+, I+	I, C+, CO	C+, CO-	C-, CO	R	R	R	R
11	0.1	B+, I	B+, I	B+, I	B, I-, CO, S-	B-, C-	CO-	CO	CO	CO-	R
12	0.1	B+, I	B+, I	B+, I	B+, I+, CO	B+, I+, CO	B, I, CO	B+, I, CO	B, CO	CO	R
13	0.05	B+, I	B+, I	B+, I, CO	B, I+, CO, S	B, I+, CO, S	B-, I, CO	CO-	R	R	R
14	0.05	B+, I	B+, I	B+, I+	B+, I+, CO	B, CO	B, CO	B-, CO	CO	R	R
15	0.05	B-	B+, I	B+, I	B+, I+, CO, S+	B+, I+, CO, S	B, I, CO	B, CO	B-	R	R
16	0.05	B+, I	B+, I	B+, I+	B+, I+, CO, S+	B+, I+, CO, S	B, I, CO	B, CO	B, CO	R	R
17	0.05	B+, I	B+, I+	B+, I+, CO	B+, I+, CO, S+	B+, I+, CO, S	B, I, CO	B, CO	CO	R	R
18	0.05	B+, I+	B+, I+	B+, I+	B-, I+, CO	B, I, CO	B-, CO	B-, CO	CO	R	R
19	0.05	B+, I	B+, I	B+, I, CO	B+, I+, CO, S	B, I+, CO, S	B, I, CO	CO	R	R	R
20	0.05	B+, I	B+, I+	B3, I+	B+, I+, CO, S-	B+, I+, CO	B, CO	B-, CO	CO	R	R
21	0.05	B-	B+, I	B+, I	B+, I+, CO, S+	B+, I+, CO, S	B, I, CO	B, CO	B	R	R
22	0.05	B+, I	B+, I	B+, I+	B+, I+, CO, S+	B+, I+, CO, S	B, I, CO	B, CO	CO	R	R
23	0.05	B+, I	B+, I+	B+, I+, CO	B+, I+, CO, S+	B+, I+, CO, S	B, I, CO	B, CO	CO	R	R
24	0.05	B+, I+	B+, I+	B+, I+	B-, I+, CO	B, I, CO	B-, CO	B-, CO	CO	R	R
25	0.01	B-	B+	B	B	B-	C-		R	R	R
26	0.01	O	B+	B	B-, C	B-, C	C-		R	R	R
27	0.01	B-	B-	B-	C-	C-	R	R	R	R	R
28	0.01	B-	B-	B-	C-	R	R	R	R	R	R
29	0.01	O	I-	R	R	R	R	R	R	R	R
30	0.01	B-	B-	I+	C-	R	R	R	R	R	R

NOTE: See legend at end of table.

Table VII. Continued

Rabbit No	Dose	Effects during postexposure period									
		1 Day	2 Days	3 Days	6 Days	8 Days	10 Days	13 Days	15 Days	21 Days	28 Days
		Temp (°F) RH (%)	69 72	83 70	81 76	79 61		82 60			
	ml										
31	0.005	O	O	O	O	O	O	O	O	O	O
32	0.005	O	O	O	O	O	O	O	O	O	O
33	0.005	O	O	O	O	O	O	O	O	O	O
34	0.005	O	O	O	O	O	O	O	O	O	O
35	0.005	I	R	R	R	R	R	R	R	R	R
36	0.005	O	O	O	O	O	O	O	O	O	O

Legend for tables VII to IX:

B- Mild blepharitis
 B Moderate blepharitis
 B+ Severe blepharitis
 I- Mild iritis
 I Moderate iritis
 I+ Severe iritis
 CO- Mild corneal opacity

CO Moderate corneal opacity
 CO+ Severe corneal opacity
 S- Mild swelling
 S Moderate swelling
 S+ Severe swelling
 R Recovery
 O No effect

C- Mild conjunctivitis
 C Moderate conjunctivitis
 C+ Severe conjunctivitis
 E- Mild erythema
 E Moderate erythema
 E+ Severe erythema
 SI Sloughing

Table VIII. Ocular Effects of Single Doses of WHITE in Rabbits (Treated Daily With Antibiotics)
at Moderate Temperatures and Humidities

Rabbit No.	Dose	Effects during postexposure period					
		1 Day	2 Days	5 Days	7 Days	14 Days	21 Days
	<i>ml</i>						
1	0.2	B+, I+, CO	B+, I+, CO	B+, I, CO	I	R	R
2	0.2	B+, I+, CO	B+, I+, CO	B+, I, CO	B+, CO	B, CO	R
3	0.2	B+, I+, CO, S	B+, I+, CO, S	B+, I, CO	B-, I, CO-	CO	R
4	0.2	B+, I+, CO, S	B+, I+, CO, S	B+, I+, CO	CO-	R	R
5	0.2	B+, I+, CO, S-	B+, I+, CO, S-	B+, I, CO	B, CO	R	R
6	0.2	B+, I+, CO, S-	B+, I+, CO, S	B+, I, CO	B, CO	R	R
7	0.1	B, I, CO-	B, I, CO-	B, I, CO	B, CO	CO	R
8	0.1	B+, I+, CO-, S-	B+, I+, CO-, S-	B+, I, CO	B+, CO	R	R
9	0.1	B, I, CO-, S-	B, I, CO-, S-	B+, CO	CO-	CO	R
10	0.1	B, I, CO, S-	B, I, CO, S-	B+, CO	R	R	R
11	0.1	B, I, CO-	B, I, CO-	B+, I, CO	B+, CO	CO	R
12	0.1	B-, I-, CO-	B-, I-, CO-	C+	R	R	R
13	0.05	B+, I, CO-	B+, I, CO-	B+, I, CO-	R	R	R
14	0.05	B+, I, CO-	B+, I, CO-	B+, I, CO	B, C+, CO	R	R
15	0.05	B, I, CO-	B, I, CO-	B, I, CO	B, CO	R	R
16	0.05	B+, I, CO-	B+, I, CO-	B, I, CO	B, CO+	B, CO	R
17	0.05	B+, I, CO-	B+, I, CO-	B, I, CO-	B-, I	R	R
18	0.05	B+, I, CO+, S+	B+, I, CO+, S+	B+, I+, CO	B+, I+, CO	B+, CO	R

NOTE: See table VII for legend.

Table IX. Ocular Effects of Single Doses of WHITE in Rabbits (Treated Daily with Antibiotics) at High Temperatures and Humidities

Rabbit No.	Dose	Effects during postexposure period					
		1 Day	2 Days	3 Days	4 Days	7 Days	10 Days
		Temp (°F) RH (%)	93 93	93 98	95 99	92 99	91 98
	ml						
1	0.05	B+, 1	B, Pus	B	B	B	B
2	0.05	B	B	B-	R	Dead	
3	0.05	B	B	B-	B-	B-	B-
4	0.01	O	O	O	O	O	O
5	0.01	B-	B-	B-	R	R	R
6	0.01	B	B	B	B	R	R
7	0.01	B-	B-	B-	R	R	R
8	0.005	O	O	O	O	O	O
9	0.005	O	O	O	O	O	O
10	0.005	O	O	O	O	O	O
11	0.005	O	O	O	O	O	O
12	0.005	O	O	O	O	O	O
13	0.005	O	O	O	O	O	O

NOTE: See table VII for legend.

Table X. Intragastric (Stomach Tube) Toxicity of WHITE in Rabbits
[5-day observation period]

Doses	Deaths	Bliss regression line			
		Deaths	Dose	95% Confidence limits	Slope
<i>ml/kg</i>		%	<i>ml/kg</i>	<i>ml/kg</i>	
6	6/6	1	0.56	0.15 to 2.02	4.9
4	6/6	16	1.04	0.49 to 2.21	
3	5/6	30	1.30	0.72 to 2.36	
1	1/6	50	1.67	1.02 to 2.71	
0.5	0/6	84	2.66	1.49 to 4.74	
		99	4.98	1.73 to 14.36	

Table XI. Intragastric (Stomach Tube) Toxicity of WHITE in Rats
[48-hour observation period]

Doses	Deaths	Bliss regression line			
		Deaths	Dose	95% Confidence limits	Slope
<i>ml/kg</i>		%	<i>ml/kg</i>	<i>ml/kg</i>	
8	5/6	1	1.04	0.32 to 3.40	3.9
6	4/6	16	2.30	1.30 to 4.06	
4	3/6	30	3.05	2.05 to 4.53	
3	3/6	50	4.17	3.02 to 5.76	
2	0/6	84	7.55	4.04 to 14.13	
1	0/6	99	16.74	4.78 to 58.61	
0.5	0/6				

Table XII. Toxicity of WHITE in Rats and Rabbits Following a Single Inhalation Exposure

Ct, based on total 10RDN and 2,4-D acids	Ct, calc as WHITE	C, calc as WHITE	Exposure time	Deaths		Day of death
				Rats	Rabbits	
<i>mg-min/cu m</i>	<i>mg-min/cu m</i>	<i>mg/cu m</i>	<i>min</i>			
117,180	383,179	1419	270	0/10	3/6	1, 1, 9
115,680	278,274	1576	240	0/10	2/6	5, 6
45,120	147,542	1230	120	0/10	1/6	11

Table XIII. Bliss Regression Line for Inhalation Toxicity of WHITE in Rabbits

Population dying	Ct	95% Confidence limits	
	<i>mg-min/cu m</i>		
1	8,370	636 to	110,135
16	43,842	34,060 to	56,434
30	78,659	33,563 to	184,348
50	150,982	79,358 to	287,252
84	519,947	86,473 to	3,126,350
99	2,723,560	61,916 to	119,803,810

Slope 1.85

UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

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11. SUPPLEMENTARY NOTES Riot Control and Chemical Training Agents, Chemistry and Medical Evaluation of Training Agents.		12. SPONSORING MILITARY ACTIVITY NA																			
13. ABSTRACT WHITE is an herbicide used extensively as a defoliant and weed killer. The purpose of this study was to assess the biological effects of this system in animals under conditions of moderate and high temperature and humidity. The toxicological studies performed indicate that a single, direct exposure to a spray of WHITE would not be likely to constitute a hazard to the skin nor a systemic hazard by inhalation. Contamination of the eyes by droplets as large as 0.2 ml would not be expected to produce permanent damage. Temporary irritation and corneal opacity could result from droplets 0.05 to 0.2 ml. Repeated exposures of the same skin area could result in local cutaneous damage that would be reversible when exposures were discontinued. Based on intra-gastric and oral toxicity studies in several animal species, a man would have to swallow grams-per-kilogram quantities of WHITE for a single dose to be lethal.																					
14. KEYWORDS <table border="0"> <tr> <td>Herbicide</td> <td>Inhalation hazard</td> </tr> <tr> <td>WHITE</td> <td>Rat</td> </tr> <tr> <td>TORDON 101</td> <td>Sheep</td> </tr> <tr> <td>Defoliant</td> <td>Cattle</td> </tr> <tr> <td>2,4-D Oral toxicity or ingestion hazard</td> <td>Rabbit</td> </tr> <tr> <td>Skin hazard</td> <td>Beagle</td> </tr> <tr> <td>Eye hazard</td> <td>Man</td> </tr> <tr> <td>Repeated exposures</td> <td></td> </tr> <tr> <td>Moderate and high temperatures and humidities</td> <td></td> </tr> </table>				Herbicide	Inhalation hazard	WHITE	Rat	TORDON 101	Sheep	Defoliant	Cattle	2,4-D Oral toxicity or ingestion hazard	Rabbit	Skin hazard	Beagle	Eye hazard	Man	Repeated exposures		Moderate and high temperatures and humidities	
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WHITE	Rat																				
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