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RHTG  
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184

CURRENT STATUS BOOK

PHARMACOLOGY DIVISION

INDEX

RHTG # 86,059  
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DECLASSIFICATION RECOMMENDED  
ROY ANDERSON, ANALYSIS  
Name (ADC) - Organization  
2-23-95  
Date

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MALCOLM THEISEN, ANALYSIS  
Name (ADD) - Organization  
2-28-95  
Date

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CURRENT STATUS - TOXICOLOGY

PHARMACOLOGY DIVISION

INHALATION SECTION

Section Chief  
Herbert H. Stokinger

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TOXICOLOGY INDEX

1. Calendar of Exposure-Units of the Inhalation Section
2. Revised Schedule of Personnel for Period as of March 15, 1945.
3. Project #8 - Inhalation Toxicity Studies of  $\text{TCI}_4$  Dust.
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5. Project #17 - Toxicity of  $\text{TC}_2\text{F}_2$  Dust by Inhalation
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7. Project #19 - Toxicity of  $\text{TF}_4$  by Inhalation.
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10. Project #23 - Toxicity of  $\text{T}_3\text{C}_8$  Dust by Inhalation.
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14. Project #30 - Tests of Efficiency of Respiratory Protective Devices in Atmospheres of T Compounds Containing C-216.
15. Projects #50 and #75 - Sensitive Tests (Indices) of T-Poisoning.
16. Projects #89 and #137 - Effect of T-Poisoning on Blood Clotting.
17. Project #92 - C-216 Analysis.
18. Project #93 - Staining of Phosphatase and Renal Tissue of T-Poisoned Animals.
19. Project #109 - Carbohydrate Metabolism in T and F Poisoned Animals.
20. Project #110 - Blood Potassium and  $\text{CC}_2$  in Acute T-Poisoning.
21. Project #111 - The Percentage Retention of Inhaled T Dust in the Respiratory Tract of Animals.
22. Project #113 - Approximate Inhalation Toxicity Studies.

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23. Project #120 - Inhalation Toxicity Studies of Tribnol, Chlorthane, 890, 891.
24. Project #138 - Toxicity of  $\text{Na}_2\text{T}_2\text{C}_7 \cdot 4\text{H}_2\text{O}$  Dust by Inhalation.
25. Project #139 - Toxicity of "Hi-Grade" T Ore by Inhalation.
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27. Project #141 - Toxicity of  $(\text{UN}_4)_2\text{T}_2\text{C}_7$  Dust by Inhalation.

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TOXICOLOGY

Section Chief.

Stokinger

Annex

Ass't. Chiefs:

Roberts  
Brodie

Office.

Dygert

Unit I.

Dygert, Head

T-Nitrate Dust Special Studies

a) 20 mg/m<sup>3</sup> dogs, rats  
mortality, kidney biopsy

Oberg, Control  
and Sampling

b) Tolerance studies in  
rabbits

Sanford, Service  
Mask Tests

c) Writing reports for tests on  
C-216, Tribnol. Preparation  
of tests on 816.

Unit II

Rothstein, Head

TO<sub>2</sub>F<sub>2</sub> Dust Exposure

0.2 mg/m<sup>3</sup> pre-conditioning  
exposure  
Dust retention studies  
Building of apparatus

Laskin, Control  
and Sampling

Dittman

Berkowitz

Unit III

Roberts, Head

T-Nitrate 0.2 mg/m<sup>3</sup>  
Pre-conditioning exposure

Brodie

a) Special exposure studies  
of Unit 1.  
Toxicity via respiratory-  
tree lung function tests

Bishop  
Wichser

Chemical determination on  
T-nitrate exposed animals

March 7, 1945

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Unit IV

Speigl, Head	TF <sub>6</sub> Exposure 3 mg/m <sup>3</sup> preparations for exposure studies
Schepartz	Tests of chamber-air; preparation of animals
Schlamowitz, Head	0.5 mg/m <sup>3</sup> preparations for exposures
Minor Pozzani	a) Preparation of animals b) Tests of chamber-air c) Application of enzymic method for C-216 analysis for chamber atmospheres d) Familiarization with procedures for exposure

Unit V

Weil, Head	Tribnol 15-20 ppm. preparation for exposure studies Sampling and analyzing chamber atmospheres of Tribnol, Chlorthane and improvement in methods
Horton Wilson	Application of spot-test method to Chlorthane atmospheres
a) <u>Lung Retention</u>	
Craver	
Ogi	
b) <u>Analytical Laboratory</u>	T-analysis
Cohenour, Head	a) Dust Concentration for 5 exposure units
Davis	b) Respirator c) Serum d) Foill (Lt. Tybout)
	T-analysis Glass blowing for Inhalation section (9 units)

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March 7, 1945

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PROJECT NUMBER 22

INHALATION TOXICITY STUDIES OF C-212

CURRENT STATUS

Two shifts are operating concurrently synthesizing C-212.

Personnel

	<u>1st Shift</u>	<u>2nd Shift</u>
Head	P. Hoch C. LaBelle	B. Amdur

TESTS COMPLETED

Acute pilot exposure to 14 ppm. All animals (10 mice, 10 rats, 8 rabbits, and 20 guinea pigs) died within 3 hours and 26 minutes.

TESTS PROJECTED

Acute pilot exposure to 5 ppm. Acute pilot exposures to lower concentrations to determine the concentrations for 30-day exposures.

One-year chronic exposure to concentration selected on the basis of the 30-day exposures.

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PROJECT NUMBER 21

TOXICITY OF  $\text{TO}_2$  DUST BY INHALATION

CURRENT STATUS

No work current

Personnel

None

TESTS COMPLETED

30-day exposure to  $22 \text{ mg/m}^3$  of  $\text{TO}_2$

TESTS PROJECTED

30-day exposures in 2 daily shifts

a) to  $5 \text{ mg/m}^3$  of  $\text{TO}_2$

b) to  $1 \text{ mg/m}^3$  of  $\text{TO}_2$

1 year exposures in 2 daily shifts to  
2 dust concentrations to be determined.

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c) Tissue samples

Harrison, Head

Kaplan

Lubell

d) Animal Care

Kesel, Chief

Heineinger

Kesel

Semmel

Baere

New Wing

Ass't. Chief

Cobler

Office

Henry

Unit 7

C-216 studies ( 3 mg./m<sup>3</sup>)

Eriksen, Head

Writing of reports for run #3  
(3 ppm.) and for high concentration  
pilot exposures (10,000, 1,000,  
500, 200 and 100 ppm)

Shannon

Chamber control and sampling

Unit 8B

Emergency Inhalation unit(C-816  
studies)

Weil, Head

Infra-red spectrophotometric  
analysis of C-816

Maiers

Chamber control and care of animals

Laush

Infra-red spectrophotometric  
analysis of C-216

Unit 8C

C-212 exposure studies

Hoch, Head

Synthesis of C-212  
Planning of pilot exposure at 5 ppm.

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March 7, 1945

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LaBelle                   Assisting with the synthesis of  
of C-212

Unit 9

TC14 studies at 0.1 mg./m<sup>3</sup>

Rothermel, Head       Writing the reports for run #3  
(0.3 mg./m<sup>3</sup>) and calibration of  
dust feed for the proposed run of 0.1  
mg./m<sup>3</sup>

Cobler                   Writing the reports of run #2  
(3 mg./m<sup>3</sup>)  
Planning of new chemical laboratory  
and supervision of inhalation group

Brinkman

a) Control Chamber.

Sprague, Head

Harrison

Preparation for control run

b) Tissues Samples.

Tornaben, Head

Glucose tolerance tests for Dr.  
Roberts  
Experimental surgery  
Gross autopsy of animals for unit 9

Seymour

Gross autopsy of animals from unit 9

Amdur

Office

Dygert  
Curtiss  
Henry  
Siegl

Glover

Animal Care

Kesel, Chief

Darrah  
Papke  
Mason  
VanScoyk  
Enos  
Price

March 7, 1945

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Project #8

INHALATION TOXICITY STUDIES OF  $\text{TCI}_4$ -DUST

CURRENT STATUS:

Two groups of animals will be exposed to 0.20 mg and 1.6 mg of  $\text{TCI}_4$  (0.12 mg and 1.0 mg of T-metal per cubic meter of chamber air, respectively). The pre-exposure period will start March 19, 1945. The exposure will begin April 2, 1945 and will continue for 30 days.

Animals Tested: (Taken from Planning Session #61)

Rats	20
Rabbits	10
Mice	75

Personnel:

	<u>1st Shift</u>	<u>2nd Shift</u>
Unit Heads	Rothermel and Cobler	Field
Assistants	Brinkman	Tornaben

TESTS COMPLETED:

30-day exposures to mean concentrations of 18 mg, 3.3 mg and 0.4 mg of  $\text{TCI}_4$  (11 mg, 1.9 mg and 0.26 mg of T-metal, respectively) per cubic meter of chamber air.

TESTS PROJECTED:

One-year exposure to concentrations of  $\text{TCI}_4$  selected on the basis of the 30-day exposures.

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PROJECT #16

TF<sub>6</sub> - TOXICITY BY INHALATION

CURRENT STATUS:

Exposure of two groups of animals to 3.0 mg TF<sub>6</sub>/m<sup>3</sup> and to 0.5 mg TF<sub>6</sub>/m<sup>3</sup>, respectively, is scheduled to begin simultaneously on two shifts during the week of March 11th. Animals tested at each level are: 5 dogs, 20 guinea pigs, 20 mice, 10 rabbits, 20 rats.  
Effects - See projects 89, 92, 504, 75  
Personnel

Heads \* Spiegl and Schlamowitz  
Assistants - Schepartz, Pozzani and Minor  
Personnel is divided between two shifts.

TESTS COMPLETED:

- A. Concentration-Time studies at "flood" concentrations of 10 minutes duration.
- B. Exposure of groups of animals to 20 mg TF<sub>6</sub>/m<sup>3</sup> for 30 days.

TESTS PROJECTED:

- A. Exposure of animals for 30 days to:
  - a. 0.2 mg TF<sub>6</sub>/m<sup>3</sup>
  - b. 0.1 mg TF<sub>6</sub>/m<sup>3</sup>
- B. One year exposures to 2 concentrations of compound to be determined later.

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PROJECT #17

TOXICITY OF  $\text{TO}_2\text{F}_2$  DUST BY INHALATION

CURRENT STATUS:

Groups of animals are exposed to 0.2 mg of  $\text{TO}_2\text{F}_2/\text{m}^3$ .  
Exposure began and is to continue until Monday, 4/9.

Animals Tested: (Taken from Planning Session #53)

9 dogs  
45 rabbits  
20 rats  
50 mice

Personnel: Unit Head - Rothstein  
Assistants - Dittman, Laskin, Berkowitz

TESTS COMPLETED: Exposure for 30 days to

- a) 12  $\text{mg}/\text{m}^3$   $\text{TO}_2\text{F}_2$
- b) 2.5  $\text{mg}/\text{m}^3$  of air
- c) 0.65  $\text{mg}/\text{m}^3$

TESTS PROJECTED:

One-year exposure to two concentrations to be selected, probably 0.2 and 1.0 mg of  $\text{TO}_2\text{F}_2$ -dust per cubic meter of air. The two concentrations to be run concurrently on a two daily shift basis.

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PROJECT #18

TOXICITY OF T-NITRATED DUST BY INHALATION

CURRENT STATUS:

Groups of animals are exposed to 20 mg/m<sup>3</sup> of T-nitrate. This exposure began on 12 February in Unit I, and is to continue for 30 days.

Animals Tested: 4 dogs, 100 rats (from P.S. #57)

Effects - See Projects 93, 109, 110 and 75 and 50

Personnel: Heads: Dygert, Roberts, Brodie

Assistants: Oberg, Bishop, Laskin, Wichser

TESTS COMPLETED:  
in Unit 3

Exposure for 30 days

- a) to 4.5 mg/m<sup>3</sup> T-nitrate
- b) to 2.0 mg/m<sup>3</sup> T-nitrate
- c) to 0.5 mg/m<sup>3</sup> T-nitrate

TESTS PROJECTED:

One year exposure on a 2 daily shift basis to two dust concentrations to be selected.

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PROJECT NUMBER 19

TOXICITY OF  $TF_4$  BY INHALATION

CURRENT STATUS

No work current.

Personnel

None

TESTS COMPLETED

30-day exposure to  $22 \text{ mg/m}^3$  of  $TF_4$

TESTS PROJECTED

Exposures for 30 days to:

a)  $5 \text{ mg/m}^3$

b)  $1 \text{ mg/m}^3$

1-year exposures in 2 daily shifts to 2 concentrations of dust to be determined later.

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PROJECT NUMBER 23

TOXICITY OF  $T_3O_8$  DUST BY INHALATION

CURRENT STATUS

No current work.

Personnel

None

TESTS COMPLETED

Exposure for 30 days to 17 milligrams per cubic meter of  $T_3O_8$ .

TESTS PROJECTED

30-day exposure in 2 daily shifts to a) 5 milligrams per cubic meter  $T_3O_8$ ; b) 1 milligram per cubic meter  $T_3O_8$ . One-year exposure in 2 daily shifts to two concentrations to be selected.

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PROJECT NUMBER 24

TOXICITY OF TO<sub>2</sub> DUST BY INHALATION

CURRENT STATUS

Two, 30-day exposures performed in 2 daily shifts  
at a) 5 mg/m<sup>3</sup>  
b) 1 mg/m<sup>3</sup>

Personnel

Head - Dygert  
Assistants - Oberg, Sanford

The personnel is divided between two shifts.

TESTS COMPLETED

Thirty-day exposure to 19 mg/m<sup>3</sup>

TESTS PROJECTED

Two, 1 year exposures performed in 2 daily shifts  
at dust concentrations to be determined.

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PROJECT NUMBER 28

INHALATION TOXICITY STUDIES OF C-216

CURRENT STATUS

Groups of animals are exposed to 0.8 milligrams per cubic meter of C-216. The exposure began February 8, and is to continue for 30 days.

Animals Tested (Taken from Planning Session #56)

Dogs	5
Rabbits	30
Guinea Pigs	24
Rats	18

Personnel

	<u>1st Shift</u>	<u>2nd Shift</u>
Unit Heads	Nils Eriksen	Nathan Glover
Assistants	A. L. Shannon	Nathan Kaplan

TESTS COMPLETED

Exposure for 20 days to 30 milligrams of C-216 per cubic meter; for 30 days to 13 milligrams per cubic meter and for 30 days to 6 milligrams of C-216 per cubic meter.

TESTS PROJECTED

One-year exposure to 0.5 milligrams of C-216 per cubic meter and one-year exposure to 0.2 milligrams of C-216 per cubic meter.

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PROJECT NUMBER 29

INHALATION TOXICITY STUDIES OF HF

CURRENT STATUS

None

TESTS COMPLETED

None

TESTS PROJECTED

30-day exposure to 25 milligrams of HF per cubic meter, and 30-day exposure to 8.3 milligrams of HF per cubic meter. The exposures will begin March 26.

Animals to be Tested

Dogs	5
Rabbits	30
Guinea Pigs	24
Rats	18

Personnel

	<u>1st Shift</u>	<u>2nd Shift</u>
Unit Heads	Nils Eriksen	Nathan Glover
Assistants	A. L. Shannon	Nathan Kaplan

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PROJECT NUMBER 30

TESTS OF EFFICIENCY OF RESPIRATORY  
PROTECTIVE DEVICES IN ATMOSPHERES OF  
T COMPOUNDS CONTAINING C-216.

CURRENT STATUS

Tests on respiratory protective devices  
against C-716 and fractions are being  
made.

Personnel

Head - P. Dygert  
Assistants - Oberg, Sanford

TEST COMPLETED

Respiratory protective devices have been  
tested against dust of  $TO_2$ ,  $TO_4$ ,  $3H_2O$ ,  $T_3O_8$ ,  
 $TF_6$ ,  $TF_4$ ,  $TO_2F_2$ ,  $TO_2(NO_3)_2$ ,  $4H_2O$ ,  $(NH_4)_2T_2O_7$ ,  $4H_2O$ ,  
"Hi-grade" ore.

TESTS PROJECTED

$TO_3$  scheduled to start April 2.  
Additional tests as requested.

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PROJECTS NO. 50 and 75

SENSITIVE TESTS (INDICES) OF T-POISONING

A number of experiments have now been completed in which animals were poisoned with T administered either by inhalation or by injection and the urinary catalase and phosphatase and protein measured. Similar tests have been made on a number of industrial workers and on a number of unexposed personnel. The results show that catalase is probably the best indicator of early renal damage following T-exposure (protein being a close second) and is superior to urinary phosphatase and non-protein-nitrogen of blood.

Recently, further work has been performed to establish the validity of the tests and to answer certain objections associated with the methods that have been raised by the Chicago Group.

A study of catalase excretion in workers exposed to T-dust has been arranged. Studies of early indices of T-poisoning are being continued on representative groups of experiments in which the catalase test is proving an extremely useful guide to the course of T-toxicity resulting from mild exposure.

Early Indices of T-poisoning. Applicability of urinary catalase, phosphatase, and protein determinations in poisoning by C-616 is being established. In the case of all rabbits tested to date, there was a rise in catalase values preliminary to death. The C-216 in the C-616 molecule does not appear to affect catalase determinations. Phosphatase and protein results were less conclusive because of the acute nature of the exposure.

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PROJECT NO. 89 and 137

EFFECT OF T POISONING ON BLOOD CLOTTING

CURRENT STATUS.

This experiment is being carried out by Dr. Field who is now assembling the necessary apparatus. No results are available as yet.

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PROJECT NO. 92

C-216 ANALYSIS

Mr. Schlamowitz has demonstrated the inhibition of liver esterase activity by C-216. This effect was applied to the quantitative determination of C-216 in aqueous solution. Comparison with the chemical method has been quite satisfactory. Application of the enzymatic method of C-216 analysis to sampling of chamber air containing C-216 has been made successfully.

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Project No. 93

STAINING OF PHOSPHATASE AND RENAL TISSUE OF  
T POISONED ANIMALS

CURRENT STATUS. No results have been obtained to date.

R. G. Metcalf

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PROJECT NO. 109

CARBOHYDRATE METABOLISM IN T AND F  
POISONED ANIMALS

A study has been divided into experiments on rats and dogs,  
and each experiment is composed of several parts.

Rat Experiment

- Part I In this experiment in which rats were exposed to  $\text{TCI}_4$  dust, data on blood glucose and the rate of formation of glycogen have been obtained as well as the necessary control data. Blood glucose remained at a higher level and the rate of glycogen formation in both liver and muscle was lower in exposed animals than in the controls.
- Part II The study on rats exposed to T-nitrate on which similar tests are being made is nearing completion.
- Part III Similar tests on rats exposed to H(CQ16) have begun.
- Part IV A study of alloxan diabetes in rats for the purpose of comparing the disturbance in carbohydrate metabolism to that caused by T has not yet been started.

Dog Experiment

- Part I 4 dogs exposed to T-nitrate ( $2 \text{ mg./m}^3$ ) exhibited an exaggerated blood glucose level within 15 and 30 minutes but not after 1 hour after the injection of glucose as a result of 2-week exposure. The injection of sodium carbonate reduced the glucose tolerance levels toward normal levels.
- Part II Another group of 4 dogs exposed to T-nitrate ( $20 \text{ mg./m}^3$ ) after 4 days of exposure exhibited high blood glucose values as long as 2 hours after the test glucose injection. Lactic and pyruvic acid values differ from those in the control period.
- Part III Another group of 4 dogs being similarly studied following exposure to H(C-216).

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PROJECT NO. 110

BLOOD POTASSIUM AND CO<sub>2</sub> IN ACUTE T POISONING

The K and CO<sub>2</sub> levels of the blood have been studied in 4 dogs and 100 rats exposed to an atmosphere containing approximately 20 milligrams of T-nitrate per cubic meter (Planning Session #57). The 30-day exposure period was concluded on March 17, and as yet all the data are not available.

The CO<sub>2</sub> content in the experimental dogs showed a marked decrease after 3 of 4 days of exposure, but after injections of either glucose or sodium bicarbonate (see summary of project #109), the CO<sub>2</sub> content increased somewhat but not to the original level. From the data available at this time, it is difficult to evaluate slight fluctuations in the potassium level of the dog.

The rats were divided into 5 groups, one serving as a control group and the others receiving diets supplemented with sodium bicarbonate, sodium citrate, potassium bicarbonate, or potassium citrate. The blood CO<sub>2</sub> level was determined twice during the exposure period, but no marked changes were observed. The blood potassium levels are not available at this time. Studies will be started in the near future concerning the effect of T-poisoning on the blood potassium in rabbits.

Lung function studies are still pending a study of suitable experimental methods and also a formal project proposal.

D. G. Brodie

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PROJECT NO. 111

THE PERCENTAGE RETENTION OF INHALED T DUST  
IN THE RESPIRATORY TRACT OF ANIMALS

CURRENT STATUS.

Apparatus is partially completed and calibrated and partially under construction. Construction and final calibration will be completed in a few weeks.

RESULTS.

The apparatus as designed has been shown to measure the respiratory rate and air turnover of rabbits with 97% accuracy, without imposing resistance on the respiratory system over a range of air turnover of 300 to 800 ml/min. and respiratory rates of 30 to 150 per minute. The apparatus is designed so that the dust concentration of inspired and expired air may be determined without interfering with the above measurements.

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PROJECT #113

APPROXIMATE INHALATION TOXICITY STUDIES

CURRENT STATUS:

14-hour exposures are being carried on with C-816 and C-716; foreshot, crude and distilled main body and tailings as furnished. 10 rats, 10 mice and 10 guinea pigs are exposed in each test.

Personnel: Head - C. S. Weil  
Assistants - I. Slotnik, R. Maiers, G. Laush

TESTS COMPLETED:

C-212 exposures to 8000, 800, 80, 8 and 3 ppm  
T-1 exposures to 56000, 21000, 5000 and 2000 ppm  
P-539 exposures to 12850, 1000, 500, 100 and 50 ppm  
C-816-1 exposures to 1000, 500, 300 and 100 ppm  
C-816-2 foreshot exposures to 500, 250 and 100 ppm  
C-816 crude exposures to 500, 250, 100 and 50 ppm  
C-816-2 exposures to 1000, 625, 300 and 250 ppm  
C-716-2 exposures to 5000, 800 and 150 ppm

TESTS PROJECTED:

As requested

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PROJECT #120

INHALATION TOXICITY STUDIES OF TRIBNOL, CHLORTHANE, 890, 891

CURRENT STATUS:

Animals are exposed to 15 ppm of Tribno. This exposure began 2-20-45 and is to continue for thirty days.

Animals Tested: 5 dogs, 6 cats, 12 rabbits,  
30 guinea pigs, 100 rats, 100 mice.  
(taken from Planning Session #60)

Personnel: Head: Weil  
Assistants: Horton, Laush, Wilson

TESTS COMPLETED:

A. Acute CT-Studies, completed

1. Tribnol - Pilot toxicity exposures to 20, 36, 150, 370 and 700 ppm.
2. Chlorthane - Pilot toxicity exposures to 20, 50, 85 and 100 ppm.
3. 890- Pilot toxicity exposures to 20, 40, 100, 200, 350, 400, 500, 600, 700, 850, 900, 1000, 1500, 2000, 3000, 3500 and 4500 ppm.

B. Thirty day studies completed or in progress.

1. Tribnol - 30 day exposure to 100 ppm
- 1a. Repeat 30-day exposure to 100 ppm (Tribnol)
2. 890 - 30-day exposure to 50 ppm.
3. 890- 30-day exposure to 20 ppm.
4. 891 - 30-day exposure to 70 mg/m<sup>3</sup>.
5. Tribnol - 9-day exposure to 20 ppm.
6. Tribnol - 30-day exposure to 15 ppm.

TESTS PROJECTED:

Control 30-day exposure to air only to provide data for the comparison of mortality, weight, blood cellular and chemical and pathology changes with those of exposed animals.

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PROJECT #138

TOXICITY OF  $\text{Na}_2\text{T}_2\text{O}_7 \cdot 4\text{H}_2\text{O}$ -DUST BY INHALATION

CURRENT STATUS: No work current

Personnel: None

TESTS COMPLETED: 30-day exposure to  $20 \text{ mg/m}^3$  of  $\text{Na}_2\text{T}_2\text{O}_7$

TESTS PROJECTED: 30-day exposures

- a) to  $40 \text{ mg/m}^3$  of  $\text{Na}_2\text{T}_2\text{O}_7$
- b) to  $5 \text{ mg/m}^3$  of  $\text{Na}_2\text{T}_2\text{O}_7$
- c) to  $1 \text{ mg/m}^3$  of  $\text{Na}_2\text{T}_2\text{O}_7$

1 year exposures to two dust concentrations to be determined later. Work to be done on the two concentrations concurrently on a two-shift basis.

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PROJECT #139

TOXICITY OF "HI-GRADE" T CRE BY INHALATION

CURRENT STATUS: No work current

Personnel: None

TESTS COMPLETED: 30-day exposure to 20 mg/m<sup>3</sup> of Hi-Grade T Cre

TESTS PROJECTED: 30-day exposures

- a) to 5 mg/m<sup>3</sup> of Hi-Grade T Cre
- b) to 1 mg/m<sup>3</sup> of Hi-Grade T Cre

1 year exposures in 2 daily shifts to two dust concentrations to be determined.

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PROJECT #14C

TOXICITY OF  $\text{TO}_4 \cdot 3\text{H}_2\text{O}$ -DUST BY INHALATION

CURRENT STATUS: No work current.

Personnel: none

TESTS COMPLETED: 30-day exposure to  $20 \text{ mg}/\text{m}^3$  of  $\text{TO}_4$

TESTS PROJECTED: 30-day exposures to

- a)  $5 \text{ mg}/\text{m}^3$  of  $\text{TO}_4$
- b)  $1 \text{ mg}/\text{m}^3$  of  $\text{TO}_4$  in 2 daily shifts

1 year exposures performed in 2 daily working shifts  
at two dust-concentrations to be determined.

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PROJECT #141

TOXICITY OF  $(\text{NH}_4)_2\text{T}_2\text{O}_7$ -DUST BY INHALATION

CURRENT STATUS: None

Personnel: None

TESTS COMPLETED:

30-day exposure to  $20 \text{ mg/m}^3$

TESTS PROJECTED:

None

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ENGINEERING  
CURRENT STATUS

Section Head  
Lt. Goring

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1188309

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ENGINEERING

SUMMARY

The engineering department servicing the toxicological sections of this project has been in operation about thirteen months to date. The greater part of the job assigned to this group, including pioneer design, construction and development, has been completed. The task of maintenance of the various units and their accessories has currently been increased somewhat due to the accelerated toxicology program.

The purpose of this report is to present, in a general manner, the scope of the work performed by this department in the past and/or present. Although it is impossible to completely generalize the subject, the various categories listed and described below should present a good indication of the overall job.

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ENGINEERING

Lt. Goring

<u>Ass't. Chief</u>	-	Murphy	Design, materials and installation of refrigerating system in the new wing to service all chambers for the summer months.
		Maier	Maintenance and operation of Chamber 4
		Bauermash	a) Setting up loading and diluting system for C-212 b) Supervision of construction of the new control chamber and cages.
		Doughty	Material list and machine shop modifications for fabrication of 3 Cascade Impactors
		Wolf	Operation and maintenance of Chambers 5, 9, and 8B.
		Same	a) Setting up of sampling unit for spot tests of tribnol and chlorthane b) Setting up of HF feeding system
		Lehman Craddock Monahan	Engineering drafting

March 7, 1945

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ANALYTICAL SECTION  
PHARMACOLOGY DIVISION  
CURRENT STATUS

Dr. John F. Flagg  
Section Head

1188312

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ANALYTICAL SECTION

Current Personnel - Job Schedule

Chief of Section: Dr. J. F. Flagg  
Assistant Chiefs: Dr. F. A. Smith and Dr. A. T. Tarbell

DIVISION I

Routine Analytical Laboratory

<u>PERSONNEL</u>	<u>DUTIES PERFORMED</u>
Lucas, Doris	Dishwashing and Cleaning
Morabito, Angelica	Blood NPN, urea, other determinations as she becomes proficient therein.
Smith, Nancy	Urinary protein, sugar, phosphatase; blood NPN, urea. Other routine analyses as soon as she becomes proficient therein.
Harrison, William	Blood NPN, urea, amino-N, phosphorus; urinary protein, sugar. Other determinations as he becomes proficient therein.
Stout, Virginia	Blood NPN, urea phosphorus, calcium; urinary protein, sugar.
Crossman, Myrtle	Blood NPN, urea, serum protein, calcium, phosphorus, phosphatase; urinary protein, sugar, phosphatase, creatinine.
O'Mally, Dorothy	Blood NPN, urea serum protein and A/G ratio, creatinine, amino nitrogen, phosphorus, calcium; urinary amino nitrogen, calcium.
Smith, Eugenia	Blood NPN, urea, serum protein, serum potassium, amino nitrogen, phosphorus. Administrative assistant.
Smith, Frank A.	Administration, choice of methods, validity of data, library research, liason between units and laboratory.
Browning, Malissa (half time)	Urinary amino nitrogen, protein, sugar.

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-2-

DIVISION II

C-216 Analysis Laboratory

<u>PERSONNEL</u>	<u>DUTIES PERFORMED</u>
Tarbell, Ann T.	Supervision of laboratory and performance of C-216 analyses.
Voss, Marion	Assistance in supervision of laboratory and performance of C-216 analyses.
Adolph, Jean	Assistance in performance of C-216 analyses.
Browning, Malissa (half time)	Performance of C-216 analyses.

DIVISION III

Research

Flagg, John F.	Supervision of laboratory; research and consultation on methods of T analysis and recovery; analysis of C-216 compounds; My and related substances.
Ware, Elinor	Synthesis and testing of organic reagents for T analysis.
Lobene, Ralph	Assistance in research projects.

May 21, 1945

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ANALYTICAL

Flagg

Ass't. Chief - Tarbell

Research:     Flagg  
                  Lobene  
                  Ware

C-216:         Tarbell  
                  Dulabahn  
                  Adolph  
                  Voss

Routine Head:  
                  Smith  
                  Stout  
                  Crossman  
                  O'Malley

Dr. Bloor

1188315

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ANALYTICAL

Chief - Flagg

Ass't. Chief- Tarbell

Research: Flagg

Head of analytical section. Director of analytical research group working on methods of  $M_x(T)$ ,  $M_y$  and  $M_z$  analysis. Consulting services for other sections.

Lobene  
Ware

Recovering traces of T from an effluent solution. Organic reagents for T analysis.

C-216 Tarbell

Direction and development of the highly specialized procedures for the quantitative micro-chemical analysis for C-216 ion in a wide variety of specimens derived from toxicological studies

Dulabahn

Research assistant. Quantitative micro-chemical analysis for C-216 ion.

Adolph

Junior research assistant. Quantitative micro-chemical analysis for C-216 ion.

Voss

Assistance in supervision of the C-216 laboratory and quantitative micro-chemical analysis for C-216 ion.

Routine Head:

Smith

Technical direction in regard to methods and technique, validity of data, and final decision in all questions.

Stout  
Crossman  
Smith  
O'Malley

All engaged in determination of pH, specific gravity, protein, sugar, creatinine, blood MPM, urea, amino N, Ca, P, K, serum proteins.

Dr. Bloor

March 7, 1945

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PHARMACOLOGY SECTION  
CURRENT STATUS

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CURRENT STATUS  
PHARMACOLOGY INDEX

1. Ingestion Toxicity Calendar
2. Project #1 - Chronic Toxicity of T-Nitrate For Rats.
3. Project #2 - Chronic Toxicity of  $TF_4$  For Rats.
4. Project #3 - Chronic Toxicity of  $TO_3$  for Rats.
5. Project #4 - Chronic Toxicity of  $TO_2$  for Rats.
6. Project #5 - Chronic Toxicity of  $T_3O_8$  for Rats.
7. Project #6 - Chronic Toxicity of  $CoF_3$  for Rats.
8. Project #7 - Chronic Toxicity of  $TO_4$  for Rats.
9. Project #8 - Chronic Toxicity of  $TCl_4$  for Rats.
10. Project #9 - Chronic Toxicity of  $TO_2F_2$  for Rats.
11. Project #10 - Chronic Toxicity of  $TO_2AC_2$  for Rats.
12. Project #11 - Chronic Toxicity of  $TO_2$  for Dogs.
13. Project #12 - Chronic Toxicity of  $TiO_3$  for Dogs.
14. Project #13 - Chronic Toxicity of  $TCl_4$  for Dogs.
15. Project #14 - Chronic Toxicity of  $TO_2F_2$  for Dogs.
16. Project #15 - Chronic Toxicity of  $TF_4$  for Dogs.
17. Project #113 - Chronic Toxicity of High Grade T Ore for Dogs.

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18. Project #129 - The Tolerance to an Acute Dose of T Induced by Repeated Administration of Small Doses of T.
19. Project #132 - *Distribution and excretion of T*
- ~~13.~~ 20. Project #148 - Lipids in T Poisoning.
20. ~~16.~~ Project #149 - The Use of the Radioactive Isotope in the Study of Distribution, Storage and Excretion of T in the Animal Body.
- xv. Project #150 - Effects of Various Agents in T-Nitrate Toxicity*

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-1-

PHARMACOLOGY

Chief - Haven

Ass't. Chiefs - Maynard  
Neuman

Ingestion: Maynard

Ingestion toxicity studies with rats on the following compounds:  $\text{TNO}_3$ ,  $\text{TO}_2\text{F}_2$ ,  $\text{TF}_4$  and  $\text{TO}_2$ . Ingestion toxicity studies with dogs on the following compounds:  $\text{TNO}_3$ ,  $\text{TO}_2\text{F}_2$ ,  $\text{TCl}_4$  and T ore.

Writing of final reports of preliminary experiments with various T compounds as fed to rats.

Richardson

General supervisor in charge of caretakers at Bronson Avenue Laboratory.

Downs

Mixing of diets for rat ingestion experiments, assisting hematology technicians with rat blood work at Bronson Avenue laboratory. Making radiographs of rats from ingestion experiments.

Meskill

Assistant Chief Animal Caretaker - In charge of feeding rats on ingestion experiments

McGuire  
Hartmann  
Miller

Animal Caretakers engaged in care and feeding of the rat breeding colony.

Plain

Animal caretaker engaged in the care of rats in the Bronson Avenue Experimental Room.

Tubbs

Secretary-stenographer for ingestion unit and for general office work at Bronson Ave. Laboratory

Maiers  
Dugan

Graphs and charts  
Typing, graphs and charts, tabulating data

Miller

Acute toxicity studies with  $\text{TNO}_3$ ,  $\text{TO}_2\text{F}_2$  and  $\text{TCl}_4$  on rats.

1188320

March 7, 1945

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PHARMACOLOGY -2-

- Skin: Orcutt  
Smith
- a) Survey of all T compounds for skin toxicology
  - b) Survey of all T compounds for eye toxicology
  - c) Detailed study of toxicology of  $\text{TO}_2(\text{NO}_3)_2$  following percutaneous absorption
  - d) Effect of various substances in protecting against poisoning by percutaneous absorption of  $\text{TO}_2(\text{NO}_3)_2$
  - e) Local skin irritation from Compound 890
  - f) Effects of Compound 891 on wound healing
  - g) Nature of C-216 burn
- Dental: Dale  
Clark  
Pagono
- Decalcifying teeth, embedding, cutting celloidin, staining sections and separating tissues from heads
- Distribution,  
Excretion and  
Storage:
- Neuman  
Fleming
- Ashing of biological samples and isolation and measurement of T therefrom. In charge of recording of data
- Carlson
- Electrolytic separation of interfering substances
- Mulryan
- Assisting Fleming in running control analyses by fluorimetric method
- Wing
- Assembling equipment for establishment of a laboratory unit for the routine analysis of industrial urine samples for T content
- Potter
- Assistant to Wing; analyzing special urine samples including control analyses on chambers
- O'Connell
- Routine determinations of rabbit urinary catalase  
Assisting with operations on rabbits
- Edwards
- Assistant to Dr. Haven and Jessie Miller; animal care and dosage; dry weights on tissues; making solutions

March 7, 1945

1188321

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PHARMACOLOGY -3-

O'Leary	In charge (with Fleming) of isolation of T from biological samples Studying solubilities of bone salt with aim of increasing size of sample from which T can be isolated
Isotope Work: <i>Haven</i>	<i>Plant urine analyses</i>
Heads: Haven Neuman Valentine	Patient relations
Crossland	The degree of unsaturation (iodine numbers) of fatty acids of liver and kidney of T-poisoned rats
Box	Cholesterol studies in rats; blood, tissues, urine
Randall	Comparison of the effect of citrates and bicarbonates on T-toxicity; citric acid method
Rothermel	Improvement of urinary phosphatase methods. Assisting with operations on rabbits Routine determinations of urinary catalase
Kaley Robinson	Routine urinary catalase by Warburg Technique for chamber animals and for rabbits from Dr. Wills and Dr. Dounce's laboratories. Assisting Lan in enzyme and tissue respiration work.
Office: Rissberger	Secretary
Technician's Assistant: McLaughlin	Washing glassware and cages
Animal Care:	
Chief: Kesel McKenzie Sullivan Cummings	

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PROJECT NUMBER 1

CHRONIC TOXICITY OF T-NITRATE FOR RATS

CURRENT STATUS

- a) Two year test: Groups of male and female rats are fed 2, 1, .5, .1, .05 and .01% T-nitrate in their diets. The feeding has been in progress for 506 days for the oldest group and is to continue for a total of 24 months.
- b) Effect of T compounds on re-production: Fifty pairs of rats are fed 2% nitrate and the re-production observed. Exposure began 17 August 1944 and is to continue for one year.
- c) Thirty day feeding test to adult rats. Groups of male and female rats, six months old, were placed on various diets on 20 Feb. 1945. The experiment is to continue for one month.
- d) One year feeding experiment. Groups of rats are to be placed on various levels of T-nitrate in the diets for periods of 3, 6, 9, and 12 months. The first group was started on the diets on 20 February 1945.

Personnel - Mr. Maynard

TESTS COMPLETED

Thirty day tests feeding male and female rats 20, 10, 5, 3, 2, 1 and .5% of T-nitrate.

TESTS PROJECTED

None

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PROJECT NUMBER 2

CHRONIC TOXICITY OF  $TF_4$  FOR RATS

CURRENT STATUS

Two year feeding test in which groups of male and female animals are fed diets containing .5, 2 and 20%  $TF_4$  respectively in their diets. The feeding began September 24, 1943 and is to continue for 24 months.

Personnel

Mr. Maynard

TESTS COMPLETED

- a) 30-day feeding test. Groups of male and female rats were fed .5, 2 and 20%  $TF_4$ .
- b) A supplementary 30-day feeding test was run in August 1944 to test the "blue-green" salt currently manufactured.

TESTS PROJECTED

None

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PROJECT NUMBER 3

CHRONIC TOXICITY OF  $TO_3$  FOR RATS

CURRENT STATUS

No work current.

Personnel

Mr. Maynard

TESTS COMPLETED

30-day feeding test in which groups of male and female rats were fed .5, 2, and 20%  $TO_3$  in their diets. This test was run in September 1943.

TESTS PROJECTED

None

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PROJECT NUMBER 4

CHRONIC TOXICITY OF TO<sub>2</sub> FOR RATS

CURRENT STATUS

Two year feeding test. Groups of male and female rats are fed 0.5, 2 and 20% of TO<sub>2</sub> respectively, in their diets. This test began in November 1943 and is to continue for 24 months.

Personnel

Mr. Maynard

TEST COMPLETED

30-day feeding tests. Groups of male and female rats were fed 0.5, 2 and 20% of TO<sub>2</sub> respectively in their diets for 30 days in July 1943.

TESTS PROJECTED

None

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PROJECT No. 5

CHRONIC TOXICITY OF  $T_3O_8$  FOR RATS

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CURRENT STATUS.

No work current.

Personnel. None

TESTS COMPLETED.

30-day feeding test in which groups of male and female rats were fed 0.5, 2 and 20 per cent of  $T_3O_8$  respectively, in the diets for 30 days. This test was begun in September 1943.

TESTS PROJECTED.

None

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PROJECT No. 6

CHRONIC TOXICITY OF  $\text{CoF}_3$  FOR RATS

CURRENT STATUS.

No work current

Personnel. Mr. Maynard

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TESTS COMPLETED.

30-day feeding tests. Groups of male and female rats were fed 0.5, 2 and 20 per cent of  $\text{CoF}_3$  in their diets for 30 days. This test was begun in September 1943.

In January 1944 a supplementary one-month study was carried out using male rats fed 0.01, 0.05 and 0.1 per cent  $\text{CoF}_3$ , respectively, in the diets.

TESTS PROJECTED.

None

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PROJECT No. 7

CHRONIC TOXICITY OF  $TO_4$  FOR RATS

CURRENT STATUS.

No work current.

~~SECRET~~

Personnel: None

TESTS COMPLETED.

- a. 30-day feeding tests in which groups of female rats were fed 0.5, 2.0, and 20 per cent  $TO_4$  in their diets. This test was run in August, 1943.
- b. 30-day feeding test in which groups of male and female rats were fed 0.25 and 1.0 per cent  $TO_4$  in their diets. This test was run in September, 1943.
- c. 30-day feeding test in which groups of male rats were fed 0.1, 0.5, and 1.0 per cent  $TO_4$  in their diets. This test was run in November, 1943.
- d. 30-day feeding test in which an additional group of male rats was fed 2.0 per cent  $TO_4$  in their diet. This test was run in November, 1943.

TESTS PROJECTED. None

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PROJECT No. 8

CHRONIC TOXICITY OF  $\text{TCI}_4$  FOR RATS

CURRENT STATUS.

No work current

Personnel: None

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TESTS COMPLETED.

- a. 30-day feeding tests in which groups of female rats were fed 0.5, 2.0, and 20 per cent  $\text{TCI}_4$  in their diets. This test was run in September, 1943.
- b. 30-day feeding test in which groups of male and female rats were fed 1.0, 1.5, and 3.0 per cent  $\text{TCI}_4$  in their diets. This test was run in November, 1943.
- c. 30-day feeding tests in which groups of male and female rats were fed 0.2, 0.5, and 1.0 per cent  $\text{TCI}_4$  in their diets. This test was started January, 1944.

TESTS PROJECTED.

None

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PROJECT No. 9

CHRONIC TOXICITY OF  $TO_2F_2$  FOR RATS

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CURRENT STATUS.

- a. 2-year feeding test in which groups of male and female rats were fed 0.25 and .50 per cent  $TO_2F_2$  in their diets. This experiment was started January, 1944, to run for two years.
- b. 2-year feeding test in which groups of male and female rats were placed on a diet of 0.01, 0.05, and 0.25 per cent  $TO_2F_2$ . This experiment was started April, 1944, to run for 2 years.
- c. 2-year feeding test in which groups of male rats were placed on a diet of 0.05, 0.10, and 0.15 per cent  $TO_2F_2$ . This experiment was started in October, 1944, to run for 2 years.

Personnel: Mr. Maynard

TESTS COMPLETED.

- a. 30-day feeding tests in which groups of male and female rats were fed 0.5, 2.0, and 20 per cent  $TO_2F_2$ . This test was run in December, 1943.
- b. 30-day feeding tests in which groups of male and female rats were fed 0.25, 1.0, and 5.0 per cent  $TO_2F_2$  in their diets. This test was run in December, 1943.
- c. 30-day feeding test in which groups of male and female rats were fed 0.05, 0.1, and 0.25 per cent  $TO_2F_2$  in their diets. This test was run in December, 1943.

TESTS PROJECTED.

None

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PROJECT No. 10

CHRONIC TOXICITY OF  $\text{TO}_2\text{AC}_2$  FOR RATS

CURRENT STATUS.

No work current

Personnel. None

TESTS COMPLETED.

30-day feeding test. Groups of male rats were fed 0.5, 2 and 20 percent  $\text{TO}_2\text{AC}_2$  in their diets. This test was begun December 28, 1943.

TESTS PROJECTED.

None.

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PROJECT NUMBER 11

CHRONIC TOXICITY OF  $TO_2$  FOR DOGS

CURRENT STATUS

No work current.

Personnel

None

TESTS COMPLETED

Thirty day feeding experiment. One dog was fed 20 g/kg/day and survived thirty days. One dog was fed 5 g/kg/day and survived thirty days.

TESTS PROJECTED

One year feeding tests in which two dogs are fed at each of three levels.

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PROJECT NUMBER 12

CHRONIC TOXICITY OF  $\text{NO}_2$  FOR DOGS

CURRENT STATUS

Two dogs are fed 0.02, .1 and .2 g/kg/day of T-nitrate respectively. This experiment was begun in January 1945, and is to continue for 12 months.

Personnel

Mr. Maynard

TESTS COMPLETED

Four dogs were fed 10 g/kg/day, 2 g/kg/day, 0.5 g/kg/day and 0.1 g/kg/day, respectively.

TESTS PROJECTED

None

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PROJECT NUMBER 13

CHRONIC TOXICITY OF  $\text{TCI}_4$  FOR DOGS

CURRENT STATUS

Two dogs are fed 0.05, .01 and .002 g/kg/day of  $\text{TCI}_4$ , respectively. This experiment was begun in January 1945 and is to continue for twelve months.

Personnel

Mr. Maynard

TESTS COMPLETED

Two dogs were fed 5 g/kg/day and 0.5 g/kg/day, respectively. Two dogs were fed 0.1 g/kg/day and 0.02 g/kg/day, respectively.

TESTS PROJECTED

None

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PROJECT NUMBER 14

CHRONIC TOXICITY OF  $\text{TO}_2\text{F}_2$  FOR DOGS

CURRENT STATUS

Two dogs are fed .0025, .001 and .0002 g/kg/day of  $\text{TO}_2\text{F}_2$ , respectively. This experiment was begun in November 1944 and is to continue for twelve months.

Personnel

Mr. Maynard

TESTS COMPLETED

Two dogs were fed 5 g/kg/day and 0.5 g/kg/day, respectively. Four dogs were fed 0.1, 0.02, 0.005 and 0.001 g/kg/day, respectively.

TESTS PROJECTED

None

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PROJECT NUMBER 15

CHRONIC TOXICITY OF  $TF_4$  FOR DOGS

CURRENT STATUS

No work current.

Personnel

None

TESTS COMPLETED

Thirty day feeding experiment. One dog was fed 20 g/kg/day, one was fed 10 g/kg/day and one fed 5 g/kg/day.

TESTS PROJECTED

One-year feeding tests in which three dogs are fed at each of three levels.

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PROJECT NUMBER 118

CHRONIC TOXICITY OF HIGH GRADE T ONE FOR DOGS

CURRENT STATUS

Thirty day feeding test. One dog is fed 5 g/kg/day. This experiment started on February 26 and is to continue for thirty days.

Personnel

Mr. Maynard

TESTS COMPLETED

A dog was fed 10 g/kg/day.

TESTS PROJECTED

One-year feeding tests in which a dog is fed at each of three levels.

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PROJECT NO. 129

THE TOLERANCE TO AN ACUTE DOSE OF T INDUCED BY REPEATED ADMINISTRATION OF SMALL DOSES OF T.

CURRENT STATUS.

Tolerance studies on young rats have been completed as follows:

No. Animals	Compound	Dose Repeated (mg*/kg)	No.	Dose Single mg*/kg.	No.	Diet	Kidneys of Survivors		
							Size	T Content	Water Cont
20	TNO <sub>3</sub>	0.33	11	5	1	fox chow	x	x	-
20	TNO <sub>3</sub>	-	-	5	1	fox chow	x	x	x
20	TNO <sub>3</sub>	0.33	11	5	1	fox chow	x	x	x
20	TNO <sub>3</sub>	-	-	5	1	fox chow	-	-	-
20	TNO <sub>3</sub>	0.33	11	5	1	0.5% bicarb.	-	-	-
20	TC <sub>2</sub> F <sub>2</sub>	-	-	1.25	1	fox chow	x	x	x
20	TO <sub>2</sub> F <sub>2</sub>	.08	11	1.25	1	foxhchow	x	x	x
20	TO <sub>2</sub> F <sub>2</sub>	-	-	2.5	1	fox chow	-	-	-
20	TO <sub>2</sub> F <sub>2</sub>	.16	11	2.5	1	fox chow	-	-	-
20	TC1 <sub>4</sub>	-	-	25.	1	fox chow	x	x	x
20	TC1 <sub>4</sub>	1.65	11	25.	1	fox chow	x	x	x

\* in terms of the salt or hydrated salt.

Personnel. In Charge - Dr. Haven  
Assistants - Virginia Edwards  
Challiss Randall

EXPERIMENTS IN PROGRESS.

1. Effect of age on tolerance.  
The tolerance of adult rats to TNO<sub>3</sub> is being determined.
2. Effect of sex on tolerance.  
Mortality is being determined on two groups of young sister-brother litter mates injected with TO<sub>2</sub>F<sub>2</sub>.
3. Duration of tolerance.  
Adult rats that have received 11 small doses of TNO<sub>3</sub> will be kept for some time before receiving a large dose.

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-2-

EXPERIMENTS PLANNED.

1. Tolerance of adult rats to  $\text{TC}_2\text{F}_2$  and  $\text{TC}_14$ .
2. Effect of sex on tolerance.  
Do males acquire tolerance to T compounds more readily than females?
3. Nature of tolerance.
  - a. How do animals that have acquire tolerance to T as the result of repeated administration of small doses handle a single large dose in respect to excretion, distribution and storage? The use of radioactive T should answer this question.
  - b. What is the effect of the development of a tolerance for T on
    - 1) the size and water content of the kidney
    - 2) degree of unsaturation of the phospholipid fatty acids of the kidney?
  - c. What is the T content of the kidney in animals that have received repeated small doses of T?

Frances Haven

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1188340

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Project No. 132

The Distribution and Excretion of T

Current project status

A fluoro-photometric method for the analysis of micro-quantities of T has been devised. A scheme for the isolation of T from biological ash has been developed. The combined techniques have been shown to give accurate analyses of T (Stand. Dev. 8%) for the following tissues: urine, feces, blood, spleen, liver, kidney, muscle, genitals, stomach, intestine, skin, carcass, and bone.

All glass metabolism cages have been constructed which will enable us to carry out complete "balance" studies.

A synthetic diet has been prepared and tested in order that the reproducibility of our experimental conditions may be improved.

In collaboration with Drs. Dounce and Wills, several preliminary physiological experiments (T clearance, T perfusion) have been conducted to ascertain the "rules" of T excretion in order that more critical experiments may be planned.

Experiments in Progress

We are attempting to increase the sensitivity of the method (below 0.5 microgm/gm.

We are building a permanent housing for the fluoro-photometer unit.

We are testing odds and ends (tissues such as, pituitary, brain, spinal cord, etc.) to make sure that in our future experiments all of the important storage sites of T will be examined.

Experiments Planned

See Revised Project Statement No. 132

Present Personnel

William Neuman  
Robert Fleming  
Anton Carlson  
John O'Leary  
Elizabeth Mulryan

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PROJECT NO. 148

LIPIDS IN T POISONING

CURRENT STATUS.

1. Total lipid of liver and kidney

a. Total lipid has been determined on the livers of the following rats:

No. Animals	Compound	Dose Small (mg/kg)	No.	Dose Large (mg/kg)	No.	Days after last injection	Dry Residue Determined *
6	TNO <sub>3</sub>	-	-	-	-	-	x
15	TNO <sub>3</sub>	-	-	5	1	10	-
8	TNO <sub>3</sub>	-	-	5	1	24	-
17	TNO <sub>3</sub>	0.33	11	5	1	23	-
18	TO <sub>2</sub> F <sub>2</sub>	0.08	11	1.25	1	28	x
14	TO <sub>2</sub> F <sub>2</sub>	-	-	1.25	1	33	x
17	TC <sub>14</sub>	1.65	11	25	1	40	x

\* for calculation of total lipid on a dry weight basis.

b. Total lipid has been determined on the kidneys of the following rats:

No. Animals	No. Determination	Compound	Dose Small (mg/kg)	No.	Dose Large (mg/kg)	No.	Days after last inject.	Dry Residue Determined
5	5	-	-	-	-	-	-	x
16	6	TNO <sub>3</sub>	-	-	5	1	10	-
17	9	TNO <sub>3</sub>	0.33	11	5	1	23	-

2. Degree of unsaturation of the phospholipid fatty acids of livers and kidney.

a. The degree of unsaturation of the phospholipid fatty acids of liver has been determined on the following rats:

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No. Animals	Number Determinations	Compound	Dose	D	Dose	No.	Days after injection
			Small (mg/kg)	Number	Large (mg/kg)		
50	10*	-	-	-	-	-	-
6	6	<del>TNO</del>	-	-	-	-	-
8	8	TNO <sub>3</sub>	-	-	5	1	24
23	23	TNO <sub>3</sub>	-	-	5	1	19
17	17	TNO <sub>3</sub>	0.33	11	5	1	23
31	7	TNO <sub>3</sub>	-	-	5	1	3

\*pooled

b. The degree of unsaturation of the phospholipid fatty acids of kidney has been determined on the following rats.

70	9*	-	-	-	-	-	-
55	10*	TNO <sub>3</sub>	-	-	5	1	3
6	6	-	-	-	-	-	-
8	8	TNO <sub>3</sub>	-	-	5	1	24
22	22	TNO <sub>3</sub>	-	-	5	1	19
17	17	TNO <sub>3</sub>	0.33	11	5	1	23

\*pooled

c. Cholesterol has been determined on the following organs and tissues of rats that received 5 mg/kg of TNO<sub>3</sub>:

liver, kidney, adrenals, whole animal, whole blood and blood serum.

Cholesterol has also been determined on blood of rats that received 2.5 mg/kg of TNO<sub>3</sub>.

EXPERIMENTS IN PROGRESS.

1. Total lipids on liver and kidney of 6 normal rats and 6 litter-mates that received 2.5 mg/kg of TNO<sub>3</sub> and were killed 6 days thereafter.
2. Degree of unsaturation of phospholipid fatty acids of liver, kidney and blood of rats in 1.
3. Effect of administration of unsaturated fats (corn oil) on mortality.
3. Cholesterol partition between red blood cells and plasma of rats at various times after 5 mg/kg of TNO<sub>3</sub>. Cholesterol ester in adrenals.

EXPERIMENTS PLANNED.

1. No more total lipids
2. Degree of unsaturation of phospholipid fatty acids of blood as a possible test for early detection of T poisoning.  
Correlation of the degree of unsaturation of phospholipid fatty acids of the kidney with the size of the dose of TNO<sub>3</sub>.  
Effect on degree of unsaturation of phospholipid fatty acids of kidney of
  - a. Administration of unsaturated fats (corn oil)
  - b. Administration of bicarbonate and citrate.

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PROJECT NO. 149

THE USE OF THE RADIOACTIVE ISOTOPE IN THE  
STUDY OF DISTRIBUTION, STORAGE AND EXCRETION  
OF T IN THE ANIMAL BODY.

CURRENT STATUS.

A tentative program for the use of the isotope has been submitted in the form of a memorandum to Dr. Hodge.

The first experiment will be carried out on kidney extracts prepared by Dr. Neuman's group for Project No. 132 on distribution of T as determined by the fluorimetric method.

At present, we have available the Pt containers in which material will be counted and are working on the technique by which samples of tissue ash dissolved in hydrochloric acid can be spread in a uniform gelatin film for counting.

Personnel.

Biochemists in charge of project: Dr. Haven  
Dr. Neuman  
M.D. in charge of human experiments: Dr. William Valentine

- \* Assistant in charge of ashing tissues,  
preparation of gelatin films and  
recording data: Marion Kaley
- \* Technician for animal care, making  
diets, quantitative care of cages  
and collection of urine and feces: Virginia Edwards  
Challiss Randall
- \* Dissector: Dr. Adler
- \* Technician for counting samples: Betty Robinson

EXPERIMENTS PLANNED.

See Memorandum to Dr. Hodge March 21, 1945.

- \* With the exception of the technician for counting samples the duties of these people will be taken care of within Dr. Neuman's group. After our program gets underway all will be needed.

Frances Haven  
March 21, 1945

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CURRENT PROJECT STATUS

PROJECT NO. 150

THE EFFECT OF VARIOUS AGENTS ON  
T NITRATE TOXICITY

Current Status.

The mortality after a 5 mg./kg. dose of T nitrate has been determined.

- a. In rats on diets containing supplements of
  - 1. choline hydrochloride and neutralized choline hydrochloride.
  - 2. disodium hydrogen phosphate
  - 3. lactic acid, sodium lactate and calcium lactate
  - 4. sodium citrate and citric acid
  
- b. In rats treated with
  - 1. renal extracts
  - 2. adrenal cortical hormones.
 Four commercial preparations have been used namely, desoxycorticosterone acetate Ciba, suprarenal cortex tablets Armour, Cortalex tablets Upjohn and suprarenal cortex liquid Armour.

Experiments in Progress.

Comparative protective action of sodium bicarbonate, sodium ditrate and citric acid administered by stomach tube to litter-mate rats on a 5 mg./kg. dose of TNO<sub>3</sub>.

Experiments Planned.

The use of combinations of agents which have been shown to cause a delay or decrease in mortality or a decrease in severity of clinical symptoms.

- e.g. suprarenal cortex with sodium bicarbonate
- "                  "          " sodium citrate
- "                  "          " essential fatty acids
- "                  "          " renal extract.

Frances Haven

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MECHANISM SECTION  
PHARMACOLOGY DIVISION

CURRENT STATUS

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Mechanism Section

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1. Project #31
2. Test #42 - Projects of the Division of Physiology
3. Project #75 - To Determine Early Tubular Damage by Detection of Enzymes in Urine.
4. Project #130 - Physical Chemistry of T Compounds in Solution.
5. Project #131A - In Vitro Studies on the Mutual Effects Produced by Interaction of T Compounds with Proteins and Enzymes.

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MECHANISM

Chief - Dounce

Ass't. Chiefs -

Wills  
Lan

In vitro work on the mutual effects caused by interaction of T compounds with enzymes and proteins. In vivo studies of protein and enzyme changes in T-poisoning.

Lan

Effect of  $T^{+++}$  on phosphorylase and phosphoglucomutase  
Effect of  $To_2Ac_2$  on respiration in tissues slices  
Effect of  $To_2Ac_2$  on adrenaline oxidase  
Oxidation of asCorbic acid by use of the tissue slice method

Wills

Kidney function studies

Main

Assists in technical phases of kidney function studies

Adler

Glomerulus studies

Fanta

T-complex formation  
General assistance in performing operations on animals

Tishkoff

Oxidation-reduction studies  
General assistance in performing operations on animals

Sunier

Physical chemical studies of nature of T ion.

March 7, 1945

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PROJECT NO. 31

Working out a micro-micro method for T to be used with body tissues and fluids.

A development of the Fluorescence method used by Hoffman for use at the 10-15 microgram level. The method as at present under trial consists in making the tissues with nitric acid, then fusing the oxidized residue with sodium fluoride and measuring the fluorescence by total extinction using a colorimeter with dark fluid (ink) in the cups.

W. R. Bloor

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TEST NO. 42

PROJECTS OF THE DIVISION OF PHYSIOLOGY

The Division of Physiology has the general project of studying the effects of T compounds on the kidney. To this end, it now has underway or projected the following investigations:

1) The pathology of acute T poisoning. The experimental work on this project has been completed; the pathological histology remains to be studied. The gross pathology was summarized in the October 1944 report. Six rabbits were used.

2) The demonstration of T in the kidneys of poisoned animals.

Use of kidneys with the greatest accumulable amount of T to demonstrate the localization of the element in the kidney. Up to six rabbits to be used.

3) Acute effects of T on kidney function. Cats to be used if possible; probably 20-30 animals will suffice to give the desired information.

4) Determination of the effect of alkali on the path of excretion of T acute experiments will be done, with the animals so arranged that urine, feces and bile can be collected separately. Probably 12 rabbits or cats will be used.

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PROJECT NO. 75

TO DETERMINE EARLY TUBULAR DAMAGE BY DETECTION OF  
ENZYMES IN URINE.

- A. Studies of catalase excretion in the urine of animals and workmen exposed to T compounds.

The method for preventing the decay of catalase activity in urine is being improved. The possible contribution of white cells to urinary catalase activity is being investigated.

Another survey of urinary catalase values of workmen in a T plant is shortly to be undertaken, using the new apparatus and testing at the plant.

Warburg determinations of the urinary catalase of several hundred chambered animals are being carried out.

- B. Studies of urinary phosphatase in animals and workmen exposed to T.

The improved phosphatase method is being applied to animals exposed to T. It is proposed to try the method in a T plant if the results of current animal experiments appear to warrant such a test.

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PROJECT NO. 130

PHYSICAL CHEMISTRY OF T COMPOUNDS IN SOLUTION

A. T complex formation

The effect of concentration of buffer anions on complex dissociation is being studied independently of the pH effect. When this study is complete, the effect of pH will be reinvestigated.

B. Oxidation-Reduction Studies Including Polarography.

The polarographic behavior of T in the presence of bicarbonate is being investigated with the object of determining redox potentials in the presence of bicarbonate. This work will be extended to include the presence of protein as well as bicarbonate, if possible.

A catalytic polarographic method for the determination of micro amounts of T also is being investigated.

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PROJECT NO. 131A

IN VITRO STUDIES ON THE MUTUAL EFFECTS PRODUCED  
BY INTERACTION OF T COMPOUNDS WITH PROTEINS AND  
ENZYMES.

The precipitating action of  $TCl_4$  neutralized to pH 5.5 with sodium acetate on proteins is being studied, as well as methods to remove  $T_4$  from combination with protein.

The action of  $T_4$  on phosphoglucomutase is being studied.

PROJECT NO. 131B

IN VIVO STUDIES OF PROTEIN AND ENZYME CHANGES  
IN T POISONING.

Respiration of tissue slices in the presence of  $T_6$  ( $\gamma_1$ ) at different pH values.

Effect of  $T_4$  on the respiration of tissue slices. Preliminary work includes a manometric study of the rate of  $T_4$  autoxidation at various pH values.

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