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PROGRESS REPORT FOR DECEMBER, 1944
Summary of Research of the Section on Pharmacology
Harold C. Hodge ✓

Inhalation Toxicity. The most striking finding from Dr. Stokinger's inhalation group is the unquestioned evidence of the toxic effects of 500 micrograms/m³ (0.5 mg./m³) of T-nitrate and of TO₂F₂, respectively. A few animals died during a month's exposure to each of these compounds at this very low dust concentration. A number of indices of poisoning have been observed; one of the newer tests in this laboratory has shown kidney function is depressed in the TO₂F₂ experiment.

Chlorthane has been studied in 14 hour exposures of groups of rats, mice and guinea pigs. 100 ppm has been shown to be a toxic concentration; 50 ppm is probably safe for short term exposures.

A new sensitive test for T poisoning may have been developed in the discovery that the amino acid excretion in urine increases after exposure to T dust in the air.

C-216. The most impressive finding of Dr. Bryan's group was the unexpected degree of toxicity of C-216 in air at 25 ppm. C-216 was lethal to rabbits, dogs and mice. Rats and guinea pigs were somewhat more resistant but showed mortalities of 50% in less than 100 exposure hours.

There is some evidence that animals in which the exposure was limited to the head suffered fewer deaths than the same species when the whole body was exposed.

C-212. With improved methods of the production of C-212 the amounts prepared are getting large enough so that we soon expect to begin preliminary toxicity experiments.

TC14. Considerable data on the toxic effects of TC14 inhalation were given. At a dust level of 18 mg./m³ TC14, rabbits and mice all succumbed, rats showed a 65% mortality but only 1 of 10 guinea pigs died. In addition to the increase in blood NPN and urea N customarily seen in T-poisoning an additional phenomenon, namely a decrease in the urinary chloride excretion, was observed.

P-539. Safe and toxic concentrations of P-539 in the air have been found for rats, guinea pigs and mice. These tests were for short exposures only.

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Ingestion Toxicity. Mr. Maynard reported a continuation of the rat feeding experiments.

20% of TO_2 in the diet was innocuous (398 days).

TF_4 was only slightly toxic at the same dietary level (428-442 days).

TO_2F_2 fed as 0.15% of the diet by weight showed toxic effects after 97 days.

T-nitrate at a level of 0.1% of the diet showed evidence of toxicity.

The breeding experiment has continued to show a marked difference between the pairs of rats fed 2% of T-nitrate and the control rats. To date, the control rats have produced 146 litters whereas the experimental rats have produced 65 litters. Furthermore, the rats receiving T-nitrate averaged smaller litters than those of the control rats.

The 30-day experiments on dogs yielded the following data:

<u>Compound</u>	<u>A dog survived the ingestion of</u>
T_{38}O	10 g./kg./day
TO_3	0.1 g./kg./day
$\text{Na}_2\text{T}_{207}$	0.1 g./kg./day
$(\text{NH}_4)_2\text{T}_{207}$	0.1 g./kg./day

The low toxicity of T_{38}O as compared to the three other compounds is evident.

Long Term Experiments. Groups of dogs are being fed various levels of TO_2F_2 . The highest dose is 0.001 g./kg./day. At the end of 30 days no toxic effects were apparent.

Skin Toxicology. Mr. Orcutt has recalculated the data for the acute skin toxicity of T-nitrate in ether solution as tested on rabbits and on guinea pigs. He has used the Method of Bliss for small samples. The dose to kill the average rabbit is about 125 mg./kg. body weight. The dose to kill the average guinea pig is about 5 g./kg. body weight. Mr. Orcutt has been studying chronic poisoning in guinea pigs. The daily application of 100 mg./kg. body weight of 13% T-nitrate solution in ether will produce a mortality of about 10% in a period of three weeks.

Dental Toxicology. Dr. Dake has reported the results of dental studies of animals exposed to triphenyl. Two points in his report may be stressed: First, the rapidity with which C-216 enters the incisor teeth of rats - it may be detected there in super-normal amounts after one to six hours exposure to triphenyl in the air. Second, the evidence of a linear relationship between the amounts of C-216 in the teeth and the duration of exposure to triphenyl.

Engineering. Lt. Goring discussed the present status of construction of dust and vapor feeds. He pointed out the difficulties, as does Captain Bryan, which we have experienced in attempts to produce a Tume. One major consideration Lt. Goring has stressed is the need for more careful study of the uniformity of air circulation and dust distribution in the chambers when very low concentrations of dust are present in the atmosphere.

Physiology. Dr. Willis reports that the inhalation of air containing a low concentration (0.5 mg./m³) of TO₂ produced a decreased kidney function only after continued exposure for two weeks.

Dr. Willis has found a lethal concentration of T for lymphocytes.

Biochemistry. Mr. O'Leary has continued his study of the origin of the color which appears in the silver filtrate of the urine of T poisoned animals. The color seems to be related to the presence of blood or of blood proteins in the urine.

Dr. Haven has recently established the fact that the livers of rats which survived acute T-poisoning were larger and had a higher water content than normal rat livers.

Dr. Haven has improved the uniformity of mortality following a standard T infection in rats dividing litter mates equally in the test groups.

The administration of a renal extract does not alter the course of acute T-poisoning in rats.

Dr. Dounce reports that xanthine oxidase is not inhibited by T-YL. With Mr. O'Connell he has been applying the catalase machine to the study of esterase in T poisoning. With Mrs. Rothermel he has shown that gastric pepsin is not inhibited by T-YL.

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With Mr. Fanta and Mr. O'Connell, Dr. Dounce has continued his investigations of the nature of the T-yl ion. In order to account for the behavior of the T ion in the body, its valence and complexing ability has been studied. Depending on the pH and the presence of various ions in solution, T-yl appears as a cation or as an anion. In either case complexes may be formed. In addition the T ion may appear as an aggregate composed of a number of T atoms. Dr. Dounce has summarized his current opinions regarding the nature of T ions.

Dr. Lan has shown that T-yl will inhibit phosphoglucomutase if the enzyme and T-yl are mixed prior to the addition of the substrate. Dr. Lan also reported that after T poisoning, rat liver lost some of its ability to oxidize glucose.

Analytical Chemistry. Dr. Farbell reports this month that 5 of 135 industrial urine samples contained 20 or more milligrams of C-216 per liter. Such a level probably is dangerous and might be attended by crippling osteosclerosis if such exposures are continued for 10 to 20 years. 10% of the samples had 10 milligrams or more of C-216 per liter.

Dr. Smith and Mrs. Burmaster report a busy month of routine chemistry. An interesting new addition to our list of methods is the series of copper sulfate solutions of carefully controlled specific gravities which are used to determine serum proteins.

Dr. Flagg's laboratory is beginning an interesting line of work, namely, the application of chromatography to T analysis.

Dr. Ware has tested a number of organic reagents to be used in the detection of T. She reports reagents which are sensitive to 1/2 to 30 mg. of T. One reagent, cacotheline, is the only one so far found which will give a color with T but not with ferric iron.

Dr. Neuman reports that from certain tissues, for example, bone, excellent T recoveries can be made using the fluorometric method. In other tissues some impurity, presumably iron, is interfering.

Are There Mental Effects of C-216 Exposure? Since we now have evidence from two different sources in which different compounds were used of mental effects of the C-216 compounds, I believe it is worth while calling attention to this reaction with the idea of keeping a watch for personality changes in men exposed to such compounds.

The observations were simple. Mr. Maynard has reported that the rats fed on the high levels of TF_4 (20% of the diet by weight) and of TO_2F_2 (0.25 and 0.5% of the diets by weight) become jumpy, are much more likely to bite the attendants than are any of the other rats and in general show agitation and discomfort. Lately we have had reports from Dr. Spiegl of the animals exposed to C-616, and from Dr. Eriksen of the animals exposed to C-216, that agitation of the sort described by Mr. Maynard had been seen after lung exposures. Sometimes the animals, especially the dogs, exhibited almost a mania.

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