

# Sharples Chemicals Inc.

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(F.Dev.-1)  
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SUBJECT: METHYL MUADS

PART Materials, Physiological Properties

SECTION TOXICITY AND TOXICOLOGY OF TETRAMETHYLTHIURAM DISULFIDE

CONTAINS NO CBI

EPA-OTS



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It was mentioned in our first report (April 15, 1946) that there is very little literature on the toxic properties of the Muads available, although about ten or twelve accelerators are being used today for various types of rubber products. As a matter of fact, only Hanzlik and Irvine's (1) paper gives lethal doses and a clinical picture of poisoning by Tetramethylthiuram Disulfide. Findings of these authors indicate intestinal absorption and systemic poisoning in contradiction to Davis' (2) assumption of non-absorption.

### METHODS AND TECHNIQUE

Rabbits weighing an average of four pounds were used in our experiment. They were kept on a standard diet.

In the feeding experiments, the powder was mixed with 20 cc. of Mazola oil each time. Hanzlik and Irvine used the dry powder.

1 cc. of Mazola oil was used for the intraperitoneal injections.

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Animals were exposed to dry powder suspended in air after elimination of particles larger than  $5\mu$ .

Irritating effects on the skin were examined on the depilated abdomen.

The methods of determining Thiuram and  $CS_2$  in air and blood have been described in our first report.

### FINDINGS

#### 1. LD 50

LD 50 was found to be 0.21 gm./kg.

#### 2. Repeated Feeding

(acute and Sub-acute Poisoning)

Nine rabbits were fed 0.1 to 0.13 gm./kg. Six animals survived four doses; one of this group five and another one six doses.

A slight decrease of hemoglobin and red blood corpuscles did not exceed the range of normal variation significantly; one rabbit (#132) showed, however, marked anisocytosis (difference in the shape and size of the red blood corpuscles). There was, in general, a moderate decrease of the number of white blood corpuscles; it was very outstanding in one animal (#162). The lymphocytes were decreased

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significantly in the two rabbits mentioned above. Otherwise, there was no significant change in the blood picture.

Glucose: No significant change.

Thymol Turbidity Test: Positive in one animal (#162).

Urea nitrogen: Increased in one rabbit (#132).

Thiuram and CS<sub>2</sub>: Negative.

It deserves mentioning that the few pathological changes were all found in two animals (#132 and #162).

Anatomical Findings: Internal organs generally pale; no hemorrhages; liver soft, pale and mottled in one rabbit (#129); kidneys slightly congested in two rabbits (#129 and #132); the urine of one animal (#132) contained blood.

Liver: Showed degenerative changes and occasionally necrotic areas. There were also congestion of the capillaries and veins and, in one case, slight infiltration of pseudo-eosinophilic cells. All these and other minor changes differed in degree.

Kidneys: Besides definite degenerative changes of the convoluted tubules, swelling and congestion of the glomeruli. Occasionally, also slight

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congestion of interstitial capillaries. These changes were rather uniform in all animals examined.

Lungs: Congested and slightly edematous.

No significant findings in other organs.

### 3. Intraperitoneal Injections

Six rabbits received 0.07 gm./kg. per dose. Four animals survived three injections; two survived four injections.

Anatomical Findings: Peritonitis with hemorrhagic exudate. Most of the organs exhibited advanced changes developed after the death of the rabbits. As far as it could be ascertained, the liver showed only minor degenerative changes and congestion. The spleen showed marked congestion of the pulp.

### 4. Inhalation

In a preliminary experiment, three rabbits were exposed for 33 days, 24 hours a day, to an air concentration increasing from 0.000008 to 0.00127 mg./l. If the amount of air inhaled by the rabbit is calculated as 0.65 l./min., the 24 hours' weights of Tetramethylthiuram Disulfide inhaled ranged from 0.008 to 1.27 mg.

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Clinical Findings: There was no definite or significant deviation from the norm. Hemoglobin and red blood corpuscles were slightly decreased in all animals. Otherwise, all morphological and chemical examinations of the blood did not reveal any pathological change.

Anatomical Findings: Gross findings normal.

The lungs of all three animals showed lymphocytic and also pseudo-eosinophilic infiltration. This infiltration was interstitial as well as peribronchial. One animal (#138) gave evidence of edema and of lymphocytic and monocytic infiltration in the mucosa and submucosa of the bronchi.

Acute interstitial and chronic focal pneumonitis was observed in #139. This animal presented also inflammatory changes in liver, heart-muscle and kidneys, and marked lymphoid hyperplasia of the spleen. Some inflammatory changes besides the changes in the lungs were shown by #138, e.g., in the kidneys (glomerulonephritis).

More significant appear degenerative changes in the liver cells found in all three animals.

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### 5. Skin Irritation

We have reported previously that the dry powder produced a moderate irritation after 24 hours of application.

### PRELIMINARY SUMMARY

The LD 50 of the product examined is higher than that reported by Hanzlik and Irvine (0.21 gm./kg. compared with 0.35 gm./kg.). Davis thinks that impurities like Diethylamine may be responsible for higher toxicity.

Our feeding experiments leave no doubt that the product is absorbed by the intestinal tract and produces systemic poisoning in high doses. However, our previous assumption that Thiuram or CS<sub>2</sub> may be found in the blood has not been confirmed. The latter is true also of inhalation since several positive results were regularly found to be due to contamination. Among the findings, a tendency to decrease of the white corpuscles was conspicuous. The histological examination showed definite degenerative and inflammatory changes in liver and kidneys; occasionally, also in other organs.

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Animals exposed to an air concentration of 0.000008 to 0.00127 mg./l. showed no definite clinical signs of poisoning. However, the histological examination of the lungs revealed inflammatory changes of the bronchi and lungs in all animals. Degenerative changes of the liver cells found in all animals are at least suspicious of being due to the exposure.

The experiment will be repeated with extended exposure to a stable air concentration. It may be remembered in this connection that the air concentration found in the plant was 0.00011 to 0.0014 mg./l.

Moderate primary skin irritation (rabbit), as reported previously, contradicts literature reports. We shall continue animal tests and also do patch tests upon the return of our students from vacation.

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BIBLIOGRAPHY

- (1) Hanzlik, P. J. and Irvine, Toxicity of Some Thioureas and Thiuram Disulfides. J. Pharmacol., 17: 349, 1921.
  
- (2) Davis, P. A., Toxic Substances in Rubber Industry -- Tetramethyl Thiuram Disulfide. Rubber Age, 30: 171, 1931.

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