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INITIAL SUBMISSION: TOXICOLOGICAL INVESTIGATION OF: THIOPHENE WITH COVER LETTER DATED 072392		
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Chemical Category		
THIOPHENE		

8(e)

CAP

(COMPLIANCE AUDIT PROGRAM)

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NOTE: Peter provides data entry in CBITS for the 8(e) CAP Documents.

8EHQ-0892-8861

"Contains NO CBI"

Monsanto

92 AUG 27 PM 2:38

ENVIRONMENT, SAFETY & HEALTH

Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167
Phone (314) 694-1000
July 23, 1992



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INIT 08/27/92

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Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 M Street, SW
Washington, DC 20460



88920007263

Attention: Section 8(e) Coordinator (CAP Agreement)

This submission is pursuant to the TSCA Section 8(e) Compliance Audit Program and CAP Agreement #8ECAP-0036.

The information included herein is characterized as follows:

Chemical Identity - THIOPHENE

Chemical CAS No. - 000112021

Information/Study Type - II,B,2,b/Acute Toxicity/Irritation Study

Information/Study Identification - Toxicological Investigation of: Thiophene
YO-65-053

Identification of Reportable Endpoint: SIGNS OF NEUROTOXICITY, MODERATELY HIGH TOXICITY IN AN INHALATION STUDY

Previous TSCA 8(e) or PMN submissions, if any, for the reference chemical can be found in Appendix A.

It should be noted that this summary is not all inclusive. Therefore, it may not highlight all adverse effects that EPA may judge to meet TSCA 8(e) reportability. This submission/report does not contain confidential business information.

Sincerely,

J. R. Condray
Director, Regulatory Management
(314) 694-8883

JUN 28 1965 374

YOUNGER LABORATORIES

Biochemists ... Pharmacologists ... Analysts

128 CLIFF CAVE ROAD
SAINT LOUIS, MO., 63129

PHONE: TILDEN 6-2540

CAS

Certificate of Analysis

000112021

June 22nd, 1965

SUBJECT -

Toxicological Investigation Of: Thiophene

Monsanto Sample Number 66

Monsanto Project Number Y-65-53

STUDY CONDUCTED FOR -

Monsanto Company, St. Louis, Missouri

EXPERIMENTAL PROCEDURE -

A) Oral LD₅₀ (Rats, Mixed Sex)

The diluted compound was fed by stomach tube to Sprague-Dawley strain albino male and female rats.

After the approximate Minimum Lethal Dose was determined, groups of male and female rats were fed in increasing doses at increments of 0.1 fractional log intervals at four levels designed to blanket the toxicity range thereby supplying data for calculation of the LD₅₀ which was done according to a modification of the method of E. J. de Beer.

Observations were made for toxic symptoms and the viscera of the animals that succumbed were examined macroscopically.

The data, together with the dilution at which the compound was fed, are shown in Table I.

B) Skin Absorption MLD (Rabbits, Mixed Sex)

The undiluted compound was applied in increasing doses at increments of 0.2 fractional log intervals to the closely clipped, intact skin of New Zealand white male and female rabbits.

The treated areas were covered with plastic strips and the animals placed in wooden stocks for periods up to twenty-four hours, after which time they were assigned to individual cages.

Observations were made for toxic symptoms and the viscera of the animals that succumbed were examined macroscopically.

The data are shown in Table II.

To: Monsanto Company
St. Louis, Missouri
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EXPERIMENTAL PROCEDURE - (Continued)

C) Skin Irritation (Rabbits)

The undiluted compound was applied to the clipped, intact skin of albino rabbits and removed after twenty-four hours. The application was covered with plastic strips to retard evaporation and avoid contamination.

Observations were made over a period of several days for irritation.

The data, scored according to the method of Draize, Woodard and Calvery (Journal of Pharm. and Exp. Therapeutics, Volume 82, December, 1944) are shown in Table III.

D) Eye Irritation (Rabbits)

0.1 Milliliter of undiluted sample was placed in the conjunctival sac of the right eye of each of three albino rabbits and observations made over a period of several days for inflammation.

The eyes were rinsed with warm isotonic saline solution after twenty-four hours.

The data, scored according to the method of Draize, et al, are shown in Table IV.

E) Vapor Inhalation (Male Rats)

Four 150-gram male rats were placed in a glass desiccator, 250 mm in diameter, and exposed to a concentrated atmosphere of vapors produced by passing a stream of air through 100 milliliters of the compound contained in a 250-milliliter Erlenmeyer flask. Vapors from the flask passed into a one liter bottle to remove droplets and then into the chamber.

Air flow through the sample was three liters per minute as measured by a calibrated rotameter. This was sufficient to violently agitate the liquid. No supplementary air was introduced inasmuch as the above supply was ample for the animals oxygen requirements.

The animals were observed for behavior and since all succumbed, the viscera were examined macroscopically.

The data are shown in Table V.

SUMMARY -

Thiophene

A) Oral LD₅₀ (Rats, Mixed Sex)

The Oral LD₅₀ for male and female rats was placed at 3120 milligrams per kilogram with lower and upper limits of 2530 to 3840 milligrams per kilogram.

The compound was classed as slightly toxic by oral ingestion in male and female rats.

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St. Louis, Missouri

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SUMMARY - (Continued)

B) Skin Absorption MLD (Rabbits, Mixed Sex)

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 3160 milligrams per kilogram and less than 5010 milligrams per kilogram.

The compound was classed as slightly toxic by skin absorption in male and female rabbits.

C) Skin Irritation (Rabbits)

The compound was classed as a moderate skin irritant when applied undiluted to intact rabbit skin.

The average maximum score was 3.6 out of a possible 8 in twenty-four hours.

D) Eye Irritation (Rabbits)

The compound was classed as a moderate eye irritant.

The average maximum score was 37.0 out of a possible 110 in twenty-four hours.

E) Vapor Inhalation (Male Rats)

All animals succumbed after twenty to twenty-five minutes of exposure.

It was considered that the vapors were extremely toxic under conditions of the test.

YOUNGER LABORATORIES

Fred M. Younger
BY: FRED M. YOUNGER

The material in this report is to be used in development of the product and may be given to responsible sales contacts, but it is not to be used by them in advertising copy. The source of this material is not to be divulged until it appears in formal publications. No exceptions to the established rule may be made without the approval of the Medical Department in St. Louis. Customers' inquiries regarding matters of toxicity are to be referred as before to the Medical Department in St. Louis for reply.

— Monsanto Chemical Company

T A B L E I

THE ORAL LD₅₀ OF 'Thiophene' FOR RATS

Sample Fed As A 50.0% Solution In Corn Oil

<u>Animal No. - Sex</u>	<u>Weight Gm.</u>	<u>Dose Mg./Kg.</u>	<u>Fate</u>
1- Female	240	2000	Survived
2- Female	240	2000	Survived
3- Male	255	2000	Survived
4- Male	235	2000	Survived
5- Female	230	2000	Survived
6- Female	240	2510	Died
7- Male	260	2510	Survived
8- Male	245	2510	Survived
9- Female	250	2510	Survived
10- Female	230	2510	Survived
11- Male	260	3160	Survived
12- Male	235	3160	Survived
13- Female	230	3160	Died
14- Female	225	3160	Survived
15- Male	255	3160	Survived
16- Male	270	3980	Died
17- Female	245	3980	Died
18- Female	255	3980	Died
19- Male	275	3980	Died
20- Male	260	3980	Died

DISCUSSION -

The Oral LD₅₀ for male and female rats was placed at 3120 milligrams per kilogram with lower and upper limits of 2530 to 3840 milligrams per kilogram.

The compound was classed as slightly toxic by oral ingestion in male and female rats.

Survival time was several hours to four days with most deaths occurring in two days.

Toxic symptoms included copious lacrimation, extreme weakness, and coma of several hours duration.

At autopsy there was renal, pulmonary, and liver hyperemia by macroscopic examination.

To: Monsanto Company
St. Louis, Missouri

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T A B L E II

THE MINIMUM LETHAL DOSE OF 'Thiophene'
BY SKIN ABSORPTION IN RABBITS

Sample Applied Undiluted

<u>Animal No. - Sex</u>	<u>Weight Kg.</u>	<u>Dose Mg./Kg.</u>	<u>Weight Change 5 Days Later Kg.</u>	<u>Fate</u>
1 - Female	2.6	794	0.0	Survived
2 - Male	2.8	1260	+ 0.1	Survived
3 - Female	2.5	2000	+ 0.1	Survived
4 - Male	3.1	3160	- 0.2	Survived
5 - Female	2.9	5010	-----	Died -- 2 Days
6 - Male	3.0	7940	-----	Died -- 2 Days

DISCUSSION -

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 3160 milligrams per kilogram and less than 5010 milligrams per kilogram.

The compound was classed as slightly toxic by skin absorption in male and female rabbits.

Survival time was two days for animals #5 and #6.

Toxic symptoms included tremors, salivation, and increasing weakness.

At autopsy the liver was dark and congested. There was also marked pulmonary hyperemia.

T A B L E II

THE MINIMUM LETHAL DOSE OF 'Thiophene'
BY SKIN ABSORPTION IN RABBITS

Sample Applied Undiluted

<u>Animal No. - Sex</u>	<u>Weight Kg.</u>	<u>Dose Mg./Kg.</u>	<u>Weight Change 5 Days Later Kg.</u>	<u>Fate</u>
1 - Female	2.6	794	0.0	Survived
2 - Male	2.8	1260	+ 0.1	Survived
3 - Female	2.5	2000	+ 0.1	Survived
4 - Male	3.1	3160	- 0.2	Survived
5 - Female	2.9	5010	-----	Died -- 2 Days
6 - Male	3.0	7940	-----	Died -- 2 Days

DISCUSSION -

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 3160 milligrams per kilogram and less than 5010 milligrams per kilogram.

The compound was classed as slightly toxic by skin absorption in male and female rabbits.

Survival time was two days for animals #5 and #6.

Toxic symptoms included tremors, salivation, and increasing weakness.

At autopsy the liver was dark and congested. There was also marked pulmonary hyperemia.

T A B L E I I I

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF 'Thiophene'

Sample Applied Undiluted

<u>Animal Number</u>	Numerical Evaluation At The End Of					
	<u>1 Hour</u>	<u>24 Hours</u>	<u>48 Hours</u>	<u>72 Hours</u>	<u>120 Hours</u>	<u>168 Hours</u>
1	2	4	3	3	2	0
2	1	3	3	2	1	0
3	1	4	3	2	2	0
Average	1.3	3.6	3.0	2.3	1.6	0.0

DISCUSSION -

The compound was classed as a moderate skin irritant when applied undiluted to intact rabbit skin.

The average maximum score was 3.6 out of a possible 8 in twenty-four hours.

Barely perceptible to well-defined erythema was noted after one hour. Overnight there was well-defined redness with very slight to slight edema for an average score of 3.6. Following removal of the application, inflammation reduced to zero in all three animals within seven days.

The compound had a defatting effect upon the epidermis causing it to flake off in thin layers after several days.

T A B L E IV

EYE IRRITATION IN RABBITS AFTER APPLICATION OF 'Thiophene'

Sample (0.1 Milliliter) Applied Undiluted

<u>Animal Number</u>	<u>Numerical Evaluation At The End Of</u>					
	<u>1 Hour</u>	<u>24 Hours</u>	<u>48 Hours</u>	<u>72 Hours</u>	<u>120 Hours</u>	<u>168 Hours</u>
1	23	35	31	22	8	2
2	25	37	31	24	12	2
3	19	29	23	15	4	0
Average	22.3	37.0	28.3	20.3	8.0	1.3

DISCUSSION -

The compound was classed as a moderate eye irritant.

The average maximum score was 37.0 out of a possible 110 in twenty-four hours.

Much discomfort was shown immediately following application.

Copious discharge, edema with slight eversion of the lids, mild erythema, and mild corneal cloudiness developed within one hour. Congestion increased somewhat in twenty-four hours at which time iris details were slightly obscured and there was a whitish exudate. Improvement followed irrigation so that within five days iris clarity was normal in two instances.

T A B L E V

INHALATION OF 'Thiophene' VAPORS BY RATS

Average Temperature Inside Chamber	76° F.
Average Relative Humidity Inside Chamber	53 %
Amount of Sample -- To Start	100 cc
Recovered	76 cc
Vaporized	(24%) 24 cc

<u>Animal No. - Sex</u>	<u>Fate</u>	<u>Observations During Exposure</u>
1 - Male	Died	Rapid, irregular breathing almost immediately ...
2 - Male	Died	Mouth partially open ...
3 - Male	Died	Gasping in ten minutes ...
4 - Male	Died	Collapse in fifteen to twenty minutes ...
		All dead in twenty-five minutes.

DISCUSSION -

All animals succumbed after twenty to twenty-five minutes of exposure. It was concluded that the vapors were extremely toxic under conditions of the test.

The vapors were only mildly inflammatory to ocular and nasal mucosae. However, the animals were rapidly weakened by the exposure and all were comatose in approximately fifteen minutes.

At autopsy there was massive pulmonary hyperemia. The liver had a bleached-like appearance.

CERTIFICATE OF AUTHENTICITY

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