PROJECT NO. Y-70-45
REPORT FILE

YOUNGER LABORATORIES
INCORPORATED
Consulting and Analytical Services
CHEMICAL . . . MICROBIOLOGICAL . . . BIOLOGICAL

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Certificate of Analysis

May 25th, 1970

SUBJECT - MCS 540

Toxicological Investigation Of: MCS 999

Monsanto Sample Number 49

Monsanto Project Number Y-70-45

STUDY CONDUCTED FOR -

Monsanto Company, St. Louis, Missouri

EXPERIMENTAL PROCEDURE -

A) Oral LD_{50} (Rats, Mixed Sex)

The undiluted 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 LD_{50} which was done according to the method of E. J. de Beer.

Observations were made for toxic signs and the viscera of the test animals were examined macroscopically.

The data 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 held in wooden stocks for periods up to twenty-four hours, after which time they were assigned to individual cages.

Observations were made for toxic signs and the viscera of the test animals were examined macroscopically.

The data are shown in Table II.

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EXPERIMENTAL PROCEDURE - (Continued)

C) Skin Irritation (Rabbits, Mixed Sex)

0.5 Milliliter of undiluted sample was applied to the clipped, intact skin of New Zealand white male and female rabbits under a one inch by one inch square patch, two single layers thick. The patches were held in place with adhesive tape. The trunk of each animal was wrapped with plastic strips, to retard evaporation and avoid contamination, for the twenty-four hour exposure period.

Observations were made over a period of seven 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, Mixed Sex)

0.1 Milliliter of undiluted sample was placed in the conjunctival sac of the right eye of each of three albino male and female rabbits and observations made over a period of seven 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) - Sample Heated To 250° F.

Six mature male rats were placed in a metal chamber of 35-liters capacity and exposed for six hours to a concentrated atmosphere of vapors produced by passing a stream of air through 146.2 grams of the compound contained in a 350-milliliter erlenmeyer flask. The sample was maintained at a temperature of 250° F. by immersing the flask in a heated sand bath.

Vapors from the flask passed into a one liter bottle to remove droplets and then into the chamber.

Air flow through the sample was 4.0 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 during exposure and for ten days following exposure. The viscera of the test animals were examined macroscopically.

The data are shown in Table V.

SUMMARY -

MCS 999

A) Oral LD_{50} (Rats, Mixed Sex)

The Oral LD_{50} for male and female rats was placed at 11,900 milligrams per kilogram with lower and upper limits of 10,900 to 12,750 milligrams per kilogram.

The compound was classed as practically non-toxic by oral ingestion in male and female rats.

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, Mixed Sex)

The compound was classed as a mild irritant when applied undiluted to intact skin of male and female rabbits.

The average maximum score was 2.0 out of a possible 8 in twenty-four hours.

D) Eye Irritation (Rabbits, Mixed Sex)

The compound was classed as a slight eye irritant in male and female rabbits.

The average maximum score was 10.6 out of a possible 110 in one hour.

E) Vapor Inhalation (Male Rats) - Sample Heated To 250° F.

All animals survived the six hour exposure as well as the following ten day observation period.

It was concluded that the vapors were practically non-toxic under conditions of the test.

YOUNGER LABORATORIES, INC.

BY: MELVIN D. BIRCH

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TABLE I

THE ORAL LD_{50} OF 'MCS 999' FOR RATS

Sample Applied Undiluted

Animal No. - Sex	Weight Gm.	Dose Mg./Kg.	Fate
1- Female	230	7,940	Survived
2- Male	270	7,940	Survived
3- Female	225	7,940	Survived
4- Male	235	7,940	Survived
5- Female	225	7,940	Survived
6- Male	260	10,000	Survived
7- Female	230	10,000	Survived
8- Male	220	10,000	Survived
9- Female	215	10,000	Survived
10- Male	225	10,000	Died
11- Female	210	12,600	Died
12- Male	205	12,600	Died
13- Female	220	12,600	Survived
14- Male	235	12,600	Died
15- Female	215	12,600	Survived
16- Male	215	15,800	Died
17- Female	205	15,800	Died
18- Male	250	15,800	Died
19- Female	220	15,800	Died
20- Male	220	15,800	Died

DISCUSSION -

The Oral LD_{50} for male and female rats was placed at 11,800 milligrams per kilogram with lower and upper limits of 10,900 to 12,750 milligrams per kilogram.

The compound was classed as practically non-toxic by oral ingestion in male and female rats.

Survival time was two to five days with most deaths occurring within three days.

Toxic signs included reduced appetite and activity for two to five days, lethargy, increasing weakness, collapse, and death.

At autopsy there was hemorrhagic lungs, jaundiced liver, and gastrointestinal inflammation.

Surviving animals were sacrificed seven days after dosing. Macroscopic examination revealed slight lung congestion in animals on upper dosage levels; the viscera of the animals on the lower dosage level appeared normal.

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TABLE II

THE MINIMUM LETHAL DOSE OF 'MCS 999'
BY SKIN ABSORPTION IN RABBITS

Sample Applied Undiluted

Animal No. - Sex	Weight Kg.	Dose Mg./Kg.	Weight Change 5 Days Later Kg.	Fate
1 - Female	2.1	3160	- 0.2	Survived
2 - Male	2.1	5010	- 0.3	Died - 10 Days
3 - Female	2.2	7940	- 0.3	Died - 11 Days
4 - Male	2.2	7940	- 0.3	Survived

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 ten to eleven days.

Toxic signs included greatly reduced appetite and activity, lethargy, increasing weakness, collapse, and death.
In fourteen days animal #1 showed 0.2 kilogram weight loss while animal #4 showed 0.7 kilogram weight loss.

At autopsy there was mottled and jaundiced liver, slight areas of lung congestion, enlarged gall bladder, and gastrointestinal inflammation. Animal #2 showed a 0.7 kilogram weight loss and animal #3 a 0.8 kilogram weight loss at time of death.

Surviving animals were sacrificed fourteen days after dosing. Macroscopic examination revealed lung congestion, liver discoloration, enlarged gall bladder, and gastrointestinal inflammation in animal #4; there was slight congestion of the lungs in animal #1.

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TABLE III

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF
'MCS 999'

Sample (0.5 Milliliter) Applied Undiluted

Animal No. - Sex	Numerical Evaluation At The End Of					
	1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1 - Female	0	2	2	1	0	0
2 - Male	0	3	2	1	0	0
3 - Female	0	1	1	0	0	0
Average	0.0	2.0	1.6	0.6	0.0	0.0

DISCUSSION -

The compound was classed as a mild irritant when applied undiluted to intact skin of male and female rabbits.

The average maximum score was 2.0 out of a possible 8 in twenty-four hours.

Observations following application --

1-Hour:	No skin changes; zero readings
24-Hours:	Barely perceptible to well-defined erythema and barely perceptible edema in one instance
48-Hours:	Barely perceptible to well-defined erythema and barely perceptible edema in one instance
72-Hours:	Barely perceptible erythema in two instances; no edema
120-Hours:	No erythema or edema; zero readings
168-Hours:	No erythema or edema; zero readings

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TABLE IV

EYE IRRITATION IN RABBITS AFTER APPLICATION OF
'MCS 999'

Sample (0.1 Milliliter) Applied Undiluted

Animal No. - Sex	Numerical Evaluation At The End Of 1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1 - Female	12	2	0	0	0	0
2 - Male	10	2	0	0	0	0
3 - Female	10	2	0	0	0	0
Average	10.6	2.0	0.0	0.0	0.0	0.0

DISCUSSION -

The compound was classed as a slight eye irritant in male and female rabbits. The average maximum score was 10.6 out of a possible 110 in one hour.

Observations following application --

Immediate:	Discomfort was slight
10-Minutes:	Slight erythema, moderate discharge; no edema
1-Hour:	Moderate erythema and moderate to copious discharge; no edema
24-Hours:	Slight erythema; no edema or discharge
48-Hours:	Eyes normal; zero readings
72- 168-Hours:	Eyes normal; zero readings

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TABLE V

INHALATION OF 'MCS 999' VAPORS BY MALE RATS

(SAMPLE HEATED TO 250°F.)

Average Temperature Inside Chamber ..... 74° F.
Average Relative Humidity Inside Chamber ..... 54 %

Amount of Sample -- To start ..... 146.2 Grams
Recovered ..... 145.8 Grams
Total Vaporized ..... 0.4 Gram (0.3 %)
Recovered from condenser. 0.0 Gram (0.0 %)
Weight of vapors entering chamber ..... 0.4 Gram (0.3 %)

Animal No. - Sex	Fate	Observations During Exposure
1 - Male	Survived	No immediate effect ...
2 - Male	Survived	Normal respiration ...
3 - Male	Survived	No nasal or ocular discharge ...
4 - Male	Survived	No weakness or drowsiness of consequence.
5 - Male	Survived	
6 - Male	Survived	

DISCUSSION -

All animals survived the six hour exposure as well as the following ten day observation period.

It was concluded that the vapors were practically non-toxic under conditions of the test.

Observations following exposure --

The animals appeared normal when removed from the chamber. The ten day observation period was uneventful. There were no bronchial rales or other evidence of respiratory complications. Weight gain was normal.

Surviving animals were sacrificed ten days following exposure. The viscera appeared normal by macroscopic examination.