YOUNGER LABORATORIES
Biochemists . . . Pharmacologists . . . Analysts

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Certificate of Analysis

July 18th, 1969

SUBJECT -

Toxicological Investigation Of: MCS 9001

Monsanto Sample Number 68

Monsanto Project Number Y-69-57

STUDY CONDUCTED FOR -

Monsanto Company, St. Louis, Missouri

EXPERIMENTAL PROCEDURE -

A) Oral LD_{50} (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 LD_{50} 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 test animals 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 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 symptoms and the viscera of the test animals were examined macroscopically.

The data are shown in Table II.

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Younger Laboratories Certificate of Analysis - Page 2 (7/18/69) - Y-69-57

EXPERIMENTAL PROCEDURE - (Continued)

C) Skin Irritation (Rabbits, Mixed Sex)

The undiluted compound was applied to the clipped, intact skin of albino male and female 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, 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 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 - Ambient Temperature (Male Rats)

Four mature male rats were placed in a metal chamber of thirty-five liters capacity and exposed for six hours to a concentrated atmosphere of vapors produced by passing a stream of air through 206.5 grams of the compound contained in a 350-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 four 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 held for ten days following exposure. The viscera of the test animals were examined macroscopically.

The data are shown in Table V.

SUMMARY -

MCS 9001

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

The Oral LD_{50} for male and female rats was placed at 1170 milligrams per kilogram with lower and upper limits of 1080 to 1270 milligrams per kilogram.

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

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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 2000 milligrams per kilogram and less than 3160 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 non-irritating when applied undiluted to intact skin of male and female rabbits.

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) - Ambient Temperature

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

It was concluded that the vapors were slightly toxic under conditions of the test.

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BY: MELVIN D. BIRCH

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TABLE I

THE ORAL LD_{50} OF 'MCS 9001' FOR RATS

Sample Fed As A 10.0% Solution In Corn Oil

Animal No. - Sex	Weight Gm.	Dose Mg./Kg.	Fate
1- Female	220	794	Survived
2- Male	225	794	Survived
3- Female	210	794	Survived
4- Male	240	794	Survived
5- Female	235	794	Survived
6- Male	255	1000	Survived
7- Female	225	1000	Survived
8- Male	220	1000	Survived
9- Female	225	1000	Survived
10- Male	240	1000	Died
11- Female	210	1260	Died
12- Male	230	1260	Survived
13- Female	215	1260	Survived
14- Male	230	1260	Died
15- Female	240	1260	Died
16- Male	220	1580	Died
17- Female	215	1580	Died
18- Male	240	1580	Died
19- Female	215	1580	Died
20- Male	225	1580	Died

DISCUSSION -

The Oral LD_{50} for male and female rats was placed at 1170 milligrams per kilogram with lower and upper limits of 1080 to 1270 milligrams per kilogram.

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

Survival time was two to six days with most deaths occurring the third day.

Toxic signs included reduced appetite and activity, increasing weakness, collapse, and death.

At autopsy there was gastrointestinal inflammation and mottled and jaundiced liver.

Surviving animals were sacrificed nine days after dosing. Slight gastrointestinal inflammation and slight discolored areas of the liver were noted on the upper dosage levels; the viscera appeared normal by macroscopic examination on the lower dosage level.

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TABLE II

THE MINIMUM LETHAL DOSE OF 'MCS 9001'
BY SKIN ABSORPTION IN RABBITS

Sample Applied Undiluted

Animal No. - Sex	Weight Kg.	Dose Mg./Kg.	Weight Change 5 Days Later Kg.	Fate
1 - Male	1.9	2000	- 0.1	Survived
2 - Female	2.0	2000	0.0	Survived
3 - Male	1.9	2000	0.0	Survived
4 - Female	2.2	3160	- 0.3	Died -- 8 Days
5 - Male	2.0	3160	0.0	Survived
6 - Female	2.4	3160	- 0.2	Died -- 5 Days
7 - Male	2.1	5010	- 0.4	Died - 10 Days
8 - Female	2.2	7940	-----	Died -- 4 Days

DISCUSSION -

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 2000 milligrams per kilogram and less than 3160 milligrams per kilogram.

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

Survival time was four to ten days.

Toxic signs included reduced appetite and activity (for three to five days in survivors), continuing weight loss, increasing weakness, collapse, and death.

At autopsy there was lung congestion, jaundiced liver, enlarged gall bladder, discolored kidneys and pancreas, and acute gastrointestinal inflammation.

Surviving animals were sacrificed fourteen days after dosing. There were areas of lung congestion, liver discoloration, and slight gastrointestinal inflammation by macroscopic examination.

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Younger Laboratories Certificate of Analysis - Page 6 (7/18/69) - Y-69-57

TABLE III

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF
'MCS 9001'

Sample Applied Undiluted

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

DISCUSSION -

The compound was classed as non-irritating when applied undiluted to intact skin of male and female rabbits.

Observations following application:

Immediate:	No apparent discomfort; zero reading
1-Hour:	Skin normal; zero reading
24- 168 Hours:	Skin normal; zero reading

Note: The compound had a drying effect on the epidermis, apparent on the fourth day, causing thin flakes to slough off in seven days.

0654463

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St. Louis, Missouri
Younger Laboratories Certificate of Analysis - Page 7 (7/18/69) - Y-69-57

TABLE IV

EYE IRRITATION IN RABBITS AFTER APPLICATION OF

'MCS 9001'

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	6	0	0	0	0
2 - Female	10	6	0	0	0	0
3 - Male	10	6	0	0	0	0
Average	10.6	6.0	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:	Great discomfort with pawing, squealing, straining against stocks, and eyes protruded
10-Minutes:	Moderate erythema, slight edema and discharge
1-Hour:	Mild to moderate erythema, slight edema, moderate discharge
24-Hours:	Mild erythema and discharge, barely perceptible edema
48-Hours:	Eye normal; zero reading
72- 168 Hours:	Eye normal; zero reading

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TABLE V

INHALATION OF 'MCS 9001' VAPORS BY RATS

Average Temperature Inside Chamber ..... 74° F.
Average Relative Humidity Inside Chamber ..... 62 %

Amount of Sample -- To start ..... 206.5 Grams
Recovered ..... 201.5 Grams
Vaporized or left in equipment ..... 5.0 Grams (2.47%)

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.

DISCUSSION -

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

It was concluded that the vapors were slightly toxic under conditions of the test.

Observations during and following exposure:

Immediate: No effect

1- 6 Hours: No apparent effect

Mild bronchial rales were present when animals were removed from the chamber.
Appetite and activity were normal within twenty-four hours.
Two animals were free from bronchial rales within seven days.
In ten days the third animal was free from bronchial rales; very slight congestion was noted in the fourth animal.
Weight gain during observation period was normal.
Surviving animals were sacrificed ten days after exposure. Macroscopic examination revealed slight areas of lung congestion; otherwise the viscera appeared normal.

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