PROJECT NO. Y-64-49
REPORT FILE

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YOUNGER LABORATORIES

Biochemists . . . Pharmacologists . . . Analysts

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Certificate of Analysis

June 15th, 1964

SUBJECT - [illegible]

Toxicological Investigation Of: MCS - 295 [illegible]

Monsanto Sample Number 57

Monsanto Project Number I-64-49

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 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 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.

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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)

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 150-milliliters of the compound contained in a 300-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 six 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 there were no deaths, all were held for ten days observation.

The data are shown in Table V.

SUMMARY -

MCS - 295

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

The Oral LD_{50} for male and female rats was placed at 4200 milligrams per kilogram with lower and upper limits of 3740 to 4700 milligrams per kilogram.

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

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 501 milligrams per kilogram and less than 794 milligrams per kilogram.

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

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SUMMARY - (Continued)

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 4.3 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 41.6 out of a possible 110 in twenty-four hours.

E) Vapor Inhalation (Male Rats)

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.

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BY: FRED M. YOUNGER

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TABLE I

THE ORAL LD_{50} OF 'MOS-295' FOR RATS

Sample Fed Undiluted

Animal No. - Sex	Weight Gm.	Dose Mg./Kg.	Rats
1- Female	210	3160	Survived
2- Female	225	3160	Survived
3- Male	230	3160	Survived
4- Male	215	3160	Survived
5- Female	220	3160	Survived
6- Female	230	3980	Died
7- Male	245	3980	Survived
8- Male	235	3980	Survived
9- Female	225	3980	Died
10- Female	220	3980	Survived
11- Male	250	5010	Died
12- Male	240	5010	Died
13- Female	215	5010	Died
14- Female	230	5010	Died
15- Male	245	5010	Died
16- Male	240	6310	Died
17- Female	230	6310	Died
18- Female	245	6310	Died
19- Male	250	6310	Died
20- Male	255	6310	Died

DISCUSSION -

The Oral LD_{50} for male and female rats was placed at 4200 milligrams per kilogram with lower and upper limits of 3740 to 4700 milligrams per kilogram.

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

Survival time was one to four days with most deaths occurring in three to four days.

Toxic symptoms included severe diarrhea, increasing weakness, tremors, and collapse.

At autopsy there was renal and liver hyperemia as well as inflammation of the gastric mucosa by macroscopic examination.

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TABLE II

THE MINIMUM LETHAL DOSE OF 'MCS-295'

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	3.1	501	0.0	Survived
2 - Female	2.6	794	- 0.2	Died -- 6 Days
3 - Male	3.2	1260	- 0.3	Died -- 7 Days
4 - Female	2.9	2000	-----	Died -- 4 Days
5 - Male	3.4	3160	- 0.3	Died -- 5 Days
6 - Female	2.8	5010	-----	Died -- 4 Days
7 - Male	3.1	7940	-----	Died -- 3 Days

DISCUSSION -

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 501 milligrams per kilogram and less than 794 milligrams per kilogram.

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

Survival time was three to seven days.

Aside from reduced appetite and moderate lethargy there was little show of toxicity until approximately twenty-four hours preceding death. Increasing weakness, tremors, and dyspnea appeared at this time.

Autopsy findings included liver with yellowish coloration and renal hyperemia.

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TABLE III

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF 'MCS-295'

Sample Applied Undiluted

Animal Number	Numerical Evaluation At The End Of 1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1	1	4	3	2	1	0
2	1	4	2	2	0	0
3	2	5	4	2	1	0
Average	1.3	4.3	3.0	2.0	0.6	0.0

DISCUSSION -

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

The average maximum score was 4.3 out of a possible 8 in twenty-four hours.

Barely perceptible to well-defined redness was present after one hour. Overnight there was moderate redness and edema for an average score of 4.3. There was no blistering. Inflammation gradually reduced following removal of the compound so that within five days only a trace of erythema remained on two animals.

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TABLE IV

EYE IRRITATION IN RABBITS AFTER APPLICATION OF 'MCS-295'

Sample (0.1 Milliliter) Applied Undiluted

Animal Number	Numerical Evaluation At The End Of					
	1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1	35	47	41	30	19	6
2	28	36	29	19	8	0
3	32	42	33	22	12	0
Average	31.6	41.6	34.3	23.6	13.0	2.0

DISCUSSION -

The compound was classed as a moderate eye irritant.

The average maximum score was 41.6 out of a possible 110 in twenty-four hours.

Discomfort was moderate immediately following application.

Mild redness and edema, moderate lacrimation, and mild dullness of the corneal area developed within one hour. Congestion increased somewhat in twenty-four hours at which time the average score was 41.6. Discharge had ceased and edema was still mild but iris details were not as clear compared to the one hour reading. Within seven days two animals were free of inflammation. Slight redness of the conjunctivae was still present on the third animal.

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TABLE V

INHALATION OF 'MCS - 295' VAPORS BY RATS

Average Temperature Inside Chamber ..... 75° F.

Average Relative Humidity Inside Chamber ..... 49 %

Amount Of Sample -- To Start ..... 150 cc
Recovered ..... 149 cc
Vaporized or left in apparatus ..... 1 cc (0.6%)

Animal No. - Sex	Fate	Observations During Exposure
1- Male	Survived	Normal breathing rate ...
2- Male	Survived	No pawing at the nose ...
3- Male	Survived	No nasal discharge ...
4- Male	Survived	No discomfort ...
5- Male	Survived	No weakness.
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.

The animals appeared unaffected by the vapors. They showed no discomfort during exposure. No inflammation of the ocular or nasal mucosae was detected when the animals were removed from the chamber.

The ten day observation period was uneventful.

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