PROJECT NO. [redacted]
REPORT FILE

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YOUNGER LABORATORIES
*Biochemists . . . Pharmacologists . . . Analysts*

128 CLIFF CAVE ROAD
SAINT LOUIS, MO., 63129
PHONE: TILDEN 6-2540

# *Certificate of Analysis*

January 12th, 1966

SUBJECT -

Toxicological Investigation Of: MCS - 404

Monsanto Sample Number 245

Monsanto Project Number Y-65-214

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) Oral MLD (Rabbits, Mixed Sex)

The undiluted compound was fed in increasing doses at increments of 0.2 fractional log intervals by stomach tube to New Zealand white male and female rabbits.

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 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 III.

D) Skin Irritation (Rabbits, Mixed Sex)

The undiluted compound was applied to the clipped, intact skin of male and female 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 IV.

E) 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 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 V.

F) Vapor Inhalation (Male Rats)

Four 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 100 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 five 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 VI.



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SUMMARY -

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

The Oral $LD_{50}$ for male and female rats was placed at 19,800 milligrams per kilogram with lower and upper limits of 17,030 to 23,165 milligrams per kilogram.

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

B) Oral MLD (Rabbits, Mixed Sex)

The Minimum Lethal Oral Dose for male and female rabbits was found to be greater than 1580 milligrams per kilogram and less than 2510 milligrams per kilogram.

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

C) Skin Absorption MLD (Rabbits, Mixed Sex)

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 1000 milligrams per kilogram and less than 1580 milligrams per kilogram.

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

D) Skin Irritation (Rabbits, Mixed Sex)

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

The average maximum score was 0.6 out of a possible 8 in twenty-four hours.

E) Eye Irritation (Rabbits, Mixed Sex)

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

The average maximum score was 11.6 out of a possible 110 in one hour.

F) 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 relatively non-toxic under conditions of the test.

YOUNGER LABORATORIES

BY: FRED M. YOUNGER

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## TABLE I

### THE ORAL $LD_{50}$ OF 'MCS-404' FOR RATS

Sample Fed Undiluted

| Animal No. - Sex | Weight Gm. | Dose Mg./Kg. | Fate |
|---|---|---|---|
| 1- Female | 230 | 12,600 | Survived |
| 2- Male | 245 | 12,600 | Survived |
| 3- Female | 220 | 12,600 | Survived |
| 4- Male | 240 | 12,600 | Survived |
| 5- Female | 225 | 12,600 | Survived |
| 6- Male | 250 | 15,800 | Survived |
| 7- Female | 235 | 15,800 | Survived |
| 8- Male | 260 | 15,800 | Survived |
| 9- Female | 240 | 15,800 | Died |
| 10- Male | 265 | 15,800 | Survived |
| 11- Female | 235 | 20,000 | Died |
| 12- Male | 255 | 20,000 | Survived |
| 13- Female | 225 | 20,000 | Died |
| 14- Male | 250 | 20,000 | Died |
| 15- Female | 230 | 20,000 | Survived |
| 16- Male | 270 | 25,100 | Died |
| 17- Female | 235 | 25,100 | Died |
| 18- Male | 255 | 25,100 | Survived |
| 19- Female | 240 | 25,100 | Died |
| 20- Male | 260 | 25,100 | Died |

DISCUSSION -

The Oral $LD_{50}$ for male and female rats was placed at 19,800 milligrams per kilogram with lower and upper limits of 17,030 to 23,165 milligrams per kilogram.

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

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

Toxic symptoms included severe diarrhea, loss of appetite, and increasing weakness.

At autopsy the gastreintestinal tract was gaseous and there was liver congestion.

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## TABLE II

### THE MINIMUM LETHAL ORAL DOSE OF 'MCS - 404' FOR RABBITS

Sample Fed Undiluted

| Animal No. - Sex | Weight Kg. | Dose Mg./Kg. | Weight Change 5 Days Later Kg. | Fate |
|---|---|---|---|---|
| 1 - Female | 2.3 | 1000 | + 0.2 | Survived |
| 2 - Male | 2.4 | 1580 | + 0.1 | Survived |
| 3 - Female | 2.6 | 2510 | - 0.2 | Died -- 5 Days |
| 4 - Male | 3.1 | 2510 | - 0.3 | Died -- 7 Days |
| 5 - Female | 2.7 | 3980 | - 0.2 | Died -- 8 Days |
| 6 - Male | 2.7 | 6310 | - 0.3 | Died -- 8 Days |

DISCUSSION -

The Minimum Lethal Oral Dose for male and female rabbits was found to be greater than 1580 milligrams per kilogram and less than 2510 milligrams per kilogram.

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

Survival time was five to eight days.
Toxic symptoms included gradual loss of appetite with increasing weakness, lethargy, and collapse.

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

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— Monsanto Chemical Company

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TABLE III

THE MINIMUM LETHAL DOSE OF 'MCS-404'
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 | 2.7 | 631 | + 0.1 | Survived |
| 2 - Male | 3.3 | 1000 | - 0.1 | Survived |
| 3 - Female | 2.5 | 1580 | - 0.2 | Died -- 6 Days |
| 4 - Male | 2.6 | 2510 | - 0.4 | Died -- 9 Days |
| 5 - Female | 2.3 | 3980 | - 0.2 | Died - 14 Days |
| 6 - Male | 2.8 | 6310 | - 0.3 | Died -- 5 Days |

DISCUSSION -

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 1000 milligrams per kilogram and less than 1580 milligrams per kilogram.

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

Survival time was five to fourteen days.
Toxic symptoms included weakness after three to six days, reduced appetite, dyspnea, collapse, and paralysis.

At autopsy there was pulmonary hyperemia; otherwise no visceral changes of consequence were noted.



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TABLE IV

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF 'MCS-404'

Sample Applied Undiluted

| Animal No. - Sex | Numerical Evaluation At The End Of 1 Hour | 24 Hours | 48 Hours | 72 Hours | 120 Hours |
|---|---|---|---|---|---|
| 1 - Male | 0 | 1 | 1 | 0 | 0 |
| 2 - Female | 0 | 0 | 0 | 0 | 0 |
| 3 - Male | 0 | 1 | 0 | 0 | 0 |
| Average | 0.0 | 0.6 | 0.3 | 0.0 | 0.0 |

DISCUSSION -

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

The average maximum score was 0.6 out of a possible 8 in twenty-four hours.

No skin changes were noted at the end of one hour. Overnight there were two instances of very slight redness with no edema for an average score of 0.6. Within seventy-two hours all animals were free of inflammation.

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TABLE V

EYE IRRITATION IN RABBITS AFTER APPLICATION OF 'MCS-404'

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 |
|---|---|---|---|---|---|
| 1 - Female | 11 | 9 | 4 | 2 | 0 |
| 2 - Male | 11 | 6 | 2 | 0 | 0 |
| 3 - Female | 13 | 8 | 4 | 4 | 0 |
| Average | 11.6 | 7.6 | 3.3 | 2.0 | 0.0 |

DISCUSSION -

The compound was classed as a slight eye irritant.
The average maximum score was 11.6 out of a possible 110 in one hour.

There was blinking but no pawing at the eyes following application.

Mild discharge, slight redness, very slight edema, and slight corneal dullness was recorded after one hour. Edema and discharge disappeared overnight. Within three days only a trace to slight erythema remained on two animals.

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## TABLE VI

### INHALATION OF 'MCS-404' VAPORS BY RATS

Average Temperature Inside Chamber ..... 74° F.

Average Relative Humidity Inside Chamber ..... 44 %

Amount of Sample -- To start ..... 100.0 cc
Recovered ..... 99.5 cc
Vaporized or left in equipment ..... 0.5 cc (0.5%)

| Animal No. - Sex | Fate | Observations During Exposure |
|---|---|---|
| 1 - Male | Survived | No immediate effect ... |
| 2 - Male | Survived | Lethargy after one hour ... |
| 3 - Male | Survived | No discomfort ... |
| 4 - Male | Survived | Normal respiration ... |
| | | No weakness. |

DISCUSSION -

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

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

With the exception of moderate lethargy, the animals showed no reaction to the vapors. Weakness was absent and no nasal or ocular inflammation was noted. Activity and appearance were normal the day following exposure and no respiratory complications developed during the ten day observation period.



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