PROJECT NO. Y-67-100
REPORT NO.

YOUNGER LABORATORIES
Biochemists . . . Pharmacologists . . . Analysts

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Certificate of Analysis

October 13th, 1967

SUBJECT -

Toxicological Investigation Of: Pydraul 230
Monsanto Sample Number 113
Monsanto Project Number Y-67-100

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 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 animals that succumbed were examined macroscopically.

The data are shown in Table II.

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EXHIBIT
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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 (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 grams 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 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 since there were no deaths, all were held for ten days observation.

The data are shown in Table V.

SUMMARY -

Pydraul 230

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

The Oral LD_{50} for male and female rats was placed at 10,500 milligrams per kilogram with lower and upper limits of 7,560 to 14,490 milligrams per kilogram.

The compound was classed as practically non-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 1260 milligrams per kilogram and less than 2000 milligrams per kilogram.

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

C) Skin Irritation (Rabbits, Mixed Sex)

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

The average maximum score was 1.6 out of a possible 8 in twenty-four hours.

D) Eye Irritation (Rabbits, Mixed Sex)

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

The average maximum score was 22.6 out of a possible 110 in one hour.

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.

YOUNGER LABORATORIES

BY: FRED M. YOUNGER

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TABLE I

THE ORAL LD_{50} OF 'Pydraul 230' FOR RATS

Sample Fed Undiluted

Animal No. - Sex	Weight Gm.	Dose Mg./Kg.	Fate
1- Female	210	7,940	Survived
2- Male	240	7,940	Survived
3- Female	215	7,940	Died
4- Male	235	7,940	Survived
5- Female	220	7,940	Survived
6- Male	240	10,000	Survived
7- Female	205	10,000	Died
8- Male	235	10,000	Died
9- Female	215	10,000	Survived
10- Male	230	10,000	Died
11- Female	220	12,600	Died
12- Male	255	12,600	Died
13- Female	210	12,600	Survived
14- Male	240	12,600	Survived
15- Female	225	12,600	Died
16- Male	250	15,800	Died
17- Female	220	15,800	Died
18- Male	235	15,800	Died
19- Female	210	15,800	Died
20- Male	230	15,800	Survived

DISCUSSION -

The Oral LD_{50} for male and female rats was placed at 10,500 milligrams per kilogram with lower and upper limits of 7,560 to 14,490 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 six days with most deaths occurring in two to three days.

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

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

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T A B L E II

THE MINIMUM LETHAL DOSE OF 'Pydraul 230'
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	2.6	501	- 0.1	Survived
2 - Female	2.4	794	- 0.1	Survived
3 - Male	2.6	1260	- 0.2	Survived
4 - Female	2.3	2000	- 0.3	Died -- 7 Days
5 - Male	2.4	3160	- 0.3	Died -- 5 Days
6 - Female	2.4	5010	- 0.2	Died -- 5 Days

DISCUSSION -

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 1260 milligrams per kilogram and less than 2000 milligrams per kilogram.

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

Survival time was five to seven days.

Toxic symptoms included lethargy and weakness in two to three days followed by tremors.

At autopsy there was pulmonary and liver hyperemia.

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T A B L E III

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF 'Pydraul 230'

Sample Applied Undiluted

	Numerical Evaluation At The End Of					
Animal No. - Sex	1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1 - Female	0	1	1	0	0	0
2 - Male	0	2	1	1	0	0
3 - Female	0	2	1	1	0	0
Average	0.0	1.6	1.0	0.6	0.0	0.0

DISCUSSION -

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

The average maximum score was 1.6 out of a possible 8 in twenty-four hours.

There were no skin changes noted the first hour. Slight to well-defined redness with no edema developed overnight. Following removal of the application, one animal was free of inflammation at the three day reading. Very slight erythema was still present on the other animals.

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T A B L E IV

EYE IRRITATION IN RABBITS AFTER APPLICATION OF 'Pydraul 230'

Sample (0.1 Milliliter) Applied Undiluted

	Numerical Evaluation At The End Of					
Animal No. - Sex	1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1 - Female	21	16	10	6	2	0
2 - Male	26	21	14	9	4	0
3 - Female	21	19	14	9	4	0
Average	22.6	18.6	12.6	8.0	3.3	0.0

DISCUSSION -

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

The average maximum score was 22.6 out of a possible 110 in one hour.

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

Copious discharge, moderate erythema, mild edema and mild corneal cloudiness was recorded after one hour. Discharge and edema improved somewhat overnight. Iris clarity was nearly normal within three days and only slight redness remained after five days.

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T A B L E V

INHALATION OF 'Pydraul 230' VAPORS BY RATS

Average Temperature Inside Chamber . . . . . 77° F.
Average Relative Humidity Inside Chamber . . . . . 61 %

Amount of Sample -- To Start ..... 100.0 Grams
Recovered ..... 99.9 Grams
Vaporized or left in equipment ..... 0.1 Gram (0.1 %)

Animal No. - Sex	Fate	Observations During Exposure
1 - Male	Survived	No immediate effect ...
2 - Male	Survived	Normal respiration ...
3 - Male	Survived	No weakness ...
4 - Male	Survived	No nasal discharge ...
		No discomfort ...
		Mild lethargy.

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.

No toxic symptoms developed during or after the six hour exposure. Nasal mucosae remained free of inflammation and no signs of discomfort were noted.
The ten day observation period was uneventful.

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