PROJECT NO. Y-68-134
REPORT FILE

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YOUNGER LABORATORIES

Biochemists . . . Pharmacologists . . . Analysts

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Certificate of Analysis

January 22nd, 1969

SUBJECT -

Toxicological Investigation Of: Santosafe 300 (MCS-528) OR-116021

Monsanto Sample Number 171

Monsanto Project Number Y-68-134

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 0.2 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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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.

SUMMARY -

Santosafe 300 (MCS-528) OR-116021

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

The Oral LD_{50} for male and female rats was placed at 4900 milligrams per kilogram with lower and upper limits of 3660 to 6560 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 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 mild irritant when applied undiluted to intact skin of male and female rabbits.

The average maximum score was 2.6 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 6.6 out of a possible 110 in one hour.

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BY: MELVIN D. BIRCH

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TABLE I

THE ORAL LD_{50} OF

'Santosafe 300 (MCS-528) OR-116021' FOR RATS

Sample Fed Undiluted

Animal No. - Sex	Weight Gm.	Dose Mg./Kg.	Fate
1- Female	190	2,510	Survived
2- Male	245	2,510	Died
3- Female	215	2,510	Survived
4- Male	250	2,510	Survived
5- Female	230	2,510	Survived
6- Male	235	3,980	Died
7- Female	205	3,980	Survived
8- Male	250	3,980	Survived
9- Female	220	3,980	Died
10- Male	245	3,980	Died
11- Female	225	6,310	Died
12- Male	250	6,310	Survived
13- Female	195	6,310	Died
14- Male	240	6,310	Died
15- Female	220	6,310	Survived
16- Male	220	10,000	Died
17- Female	205	10,000	Died
18- Male	235	10,000	Died
19- Female	215	10,000	Survived
20- Male	235	10,000	Died

DISCUSSION -

The ORAL LD_{50} for male and female rats was placed at 4900 milligrams per kilogram with lower and upper limits of 3660 to 6560 milligrams per kilogram.

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

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

Toxic symptoms included loss of appetite, weakness, and collapse.

At autopsy there was renal, liver, and pulmonary hyperemia macroscopically.

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T A B L E II

THE MINIMUM LETHAL DOSE OF 'Santosafe 300 (MCS-528) OR-116021'

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	2.5	501	+ 0.1	Survived
2 - Female	2.3	794	+ 0.1	Survived
3 - Male	2.0	1260	+ 0.1	Survived
4 - Female	2.1	2000	-----	Died -- 5 Days
5 - Male	2.4	3160	- 0.2	Died -- 7 Days
6 - Female	2.3	5010	-----	Died -- 4 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 four to seven days.

Toxic symptoms included reduced appetite and activity, increasing weakness, and collapse.

At autopsy there was liver and renal hyperemia, also hemorrhagic areas in the lungs.

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TABLE III

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF
'Santosafe 300 (MCS-528) OR-116021'

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	2	2	1	0	0
2 - Female	0	3	3	2	0	0
3 - Male	0	3	3	2	0	0
Average	0.0	2.6	2.6	1.6	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 2.6 out of a possible 8 in twenty-four hours.

No skin changes were noted in one hour.
Moderate to marked redness developed overnight. There was no edema.
Gradual improvement was noted in seventy-two hours and all animals received a score of zero within five days.

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TABLE IV

EYE IRRITATION IN RABBITS AFTER APPLICATION OF
'Santosafe 300 (MCS-528) OR-116021'

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	8	2	0	0	0	0
2 - Male	6	2	0	0	0	0
3 - Female	8	4	0	0	0	0
Average	6.6	2.6	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 6.6 out of a possible 110 in one hour.

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

Moderate erythema and lacrimation were noted after one hour.

Lacrimation had ceased and only slight redness remained after twenty-four hours.

There was no discernible corneal dullness.

All animals received a score of zero within forty-eight hours.

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