PROJECT NO. Y-63-12
REPORT FILE

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YOUNGER LABORATORIES

Biochemists . . . Pharmacologists . . . Analysts

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Certificate of Analysis

March 4th, 1963

SUBJECT - ARCCLOR

Toxicological Investigation Of: Inerteen PPO

Monsanto Sample Number 22

Monsanto Project Number Y-63-12

3/4/63
Y-63-12

STUDY CONDUCTED FOR -

Monsanto Chemical Company, St. Louis, Missouri

EXPERIMENTAL PROCEDURE -

A) Oral LD_{50} (Rats)

The undiluted compound was fed by stomach tube to Sprague-Dawley strain albino 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)

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 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.

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 (Rats)

Four 150-gram male rats were placed in a glass desiccator, 250 mm in diameter, 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 250-milliliter tall form gas washing bottle with fritted disc. Vapors from the bottle passed into a one liter bottle to remove droplets and then into the chamber. Air flow through the sample was 6 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 -

Isocyanate PPG

A) Oral LD_{50} (Rats)

The Oral LD_{50} for male and female rats was placed at 2370 milligrams per kilogram with lower and upper limits of 2095 to 2690 milligrams per kilogram.

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

B) Skin Absorption MLD (Rabbits)

The Minimum Lethal Dose by Skin Absorption in female rabbits was found to be greater than 3160 milligrams per kilogram and less than 5010 milligrams per kilogram.

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

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SUMMARY - (Continued)

C) Skin Irritation (Rabbits)

The compound was classed as a moderate skin irritant.

The average maximum score was 4.6 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 35.6 out of a possible 110 in one hour.

E) Vapor Inhalation (Rats)

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: FRED M. YOUNGER

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TABLE I

THE ORAL LD_{50} OF 'Inerteen PPO' FOR RATS

Sample Fed Undiluted

Animal No. - Sex	Weight Gm.	Dose Mg./Kg.	Fate
1- Female	220	1580	Survived
2- Female	210	1580	Survived
3- Male	255	1580	Survived
4- Male	240	1580	Survived
5- Female	215	1580	Survived
6- Female	225	2000	Survived
7- Male	245	2000	Survived
8- Male	240	2000	Died
9- Female	210	2000	Died
10- Female	220	2000	Survived
11- Male	255	2510	Died
12- Male	245	2510	Survived
13- Female	205	2510	Died
14- Female	215	2510	Died
15- Male	250	2510	Survived
16- Male	255	3160	Died
17- Female	210	3160	Died
18- Female	220	3160	Died
19- Male	255	3160	Survived
20- Male	245	3160	Died

DISCUSSION -

The Oral LD_{50} for male and female rats was placed at 2370 milligrams per kilogram with lower and upper limits of 2095 to 2690 milligrams per kilogram.

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

Survival time was approximately twenty-four hours to six days with most deaths occurring in three to five days.

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

At autopsy there was marked liver and renal hyperemia as well as pulmonary congestion.

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TABLE II

THE MINIMUM LETHAL DOSE OF 'Inorteon PPO'
BY SKIN ABSORPTION IN RABBITS

Sample Applied Undiluted

Animal No. - Sex	Weight Kg.	Dose Mg./Kg.	Weight Change 5 Days Later Kg.	Rate
1 - Female	2.3	794	+ 0.2	Survived
2 - Female	2.1	1260	0.0	Survived
3 - Female	2.4	2000	0.0	Survived
4 - Female	2.3	3160	- 0.1	Survived
5 - Female	2.5	5010	- 0.4	Died -- 5 Days
6 - Female	2.7	7940	- 0.6	Died -- 6 Days

DISCUSSION -

The Minimum Lethal Dose by Skin Absorption in female rabbits was found to be greater than 3160 milligrams per kilogram and less than 5010 milligrams per kilogram.

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

Survival time was five to six days.

The animals that succumbed lost appetite and wasted away. Movement reduced as the animals weakened but no definite paralytic symptoms were observed.

At autopsy the liver had a jaundiced-like appearance and there was pulmonary hyperemia macroscopically.

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TABLE III

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF 'I-ertsom PPO'

Sample Applied Undiluted

Animal Number	Numerical Evaluation At The End Of 1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1	2	4	4	3	2	1
2	3	5	4	2	2	1
3	3	5	5	4	2	1
Average	2.6	4.6	4.3	3.0	2.0	1.0

DISCUSSION -

The compound was classed as a moderate skin irritant.

The average maximum score was 4.6 out of a possible 8 in twenty-four hours.

After one hour there was well-defined erythema with barely perceptible swelling for an average score of 2.6 out of a possible 8. Inflammation increased overnight at which time the average score was 4.6 based upon moderate redness and slight edema. Daily improvement was noted after the application was removed. Irritation reduced to barely perceptible erythema on all animals within seven days.

TABLE IV

EYE IRRITATION IN RABBITS AFTER APPLICATION OF 'Isortron PPO'

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	37	30	21	15	8	4
2	29	21	15	9	4	0
3	41	30	19	12	6	0
Average	35.6	27.0	18.3	12.0	6.0	1.3

DISCUSSION -

The compound was classed as a moderate eye irritant.

The average maximum score was 35.6 out of a possible 110 in one hour.

Moderate discomfort was shown following application.

Within one hour there was mild edema, copious discharge, mild to moderate redness of the conjunctivae, and slight iris congestion and corneal dullness for an average score of 35.6 out of a possible 110. Discharge and cloudiness decreased overnight. Iris clarity was normal within five days and within seven days two of three animals were free of inflammation.

TABLE V

INHALATION OF 'Isotron FPO' VAPORS BY RATS

Average Temperature Inside Chamber ..... 76° F.
Average Relative Humidity Inside Chamber ..... 47 %

Animal No. - Sex	Fate	Observations During Exposure
1 - Male	Survived	Mild eye and nasal irritation after
2 - Male	Survived	twenty to thirty minutes ...
3 - Male	Survived	Moderate discomfort ...
4 - Male	Survived	Lethargy ...
		Occasional moderate dyspnea ...
		No serious weakness ...
		Slight nasal discharge.

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.

Mild inflammation of the nasal mucosa was evident when the animals were removed from the chamber. Breathing was slightly irregular but no rasping sound was detected and the animals were only mildly cyanosed. Animal behavior was practically normal, in forty-eight hours. No respiratory complications developed during the ten day observation period.