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Petitions Review Branch, DFE

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For the use of Randox (2-chloro-N,N-diallyl-acetamide) as a herbicide with negligible tolerance on various crops.

PESTICIDE PETITION No. 7F0 617
115127

Monsanto Chemical Company
St. Louis, Missouri
(PP 4-765)

Name of Drug: Randox (active principle = 2-chloro-N,N-diallyl-acetamide)
Category: Herbicide (Pesticide chemical)
Formulated Products: Randox = Emulsifiable Concentrate
Randox = 20% Granular

TOXICOLOGICAL STUDIES

TEST MATERIALS: "Randox Technical" (Emulsifiable Concentrate)

1) 90-day Subacute Oral Toxicity in Dogs. IBT # C4807 - 05/22/67

No. of animals ---------- 24 (total) 4 groups of 6 animals (3 M and 3 F)
Duration ---------- 90 days
Route ---------- Oral (mixed in the diet)
Dosage ---------- 0; 20; 62 and 200 ppm. Daily feeding.

Parameters used in this study: --

Body Weights
Food Consumption
Mortality
Behavioral Reactions
Hematological Studies
Blood Chemistry Studies
Urine Analysis
Organ Weights
Pathological Findings

Results: No significant abnormalities were found. No effect level is 200 ppm.

2) 90-day Subacute Oral Toxicity in Rats. IBT # B4806 04/21/67

No. of animals ---------- 80 (40 M and 40 F)

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Duration ---------- 21 days
Route ---------- Oral (mixed in the diet)
Dosage ---------- 0; 20; 62 and 200 ppm

Parameters used in this study: --

Body weights ---------- Only high dose rats (200 ppm) showed a minimal growth depression at the conclusion of the study.

Food Consumption ----- With the exception of females on the 200 ppm group and males in the 20 ppm group, food consumption was comparable to that of the controls. However, the differences between both affected groups did not materially affect their growth patterns.

Mortality ---------- Not significant.
Hematologic studies -- No differences between test and control animals were noted.
Clinical Chemistry --- Test and control groups were comparable.
Urine Analysis ------- No significant differences between test and control animals were founded.

Pathology:

a) Gross pathology ---- Nothing significant.
b) Micro examination -- No outstanding differences between test and control rats were noted.

Organ weights ---------- Nothing significant.

Except for minimal growth depression no adverse effects were noted. The no effect level for this study is greater then 62 ppm but somewhat less then 200 ppm; estimated at 150 ppm.

3) Acute Oral Toxicity (LD_{50}) in Rats. Scientific Ass. 11/4/53

No. of animals ---------- 21 (12 M and 9 F)
Route ---------- Oral (stomach tube)
Dosage ---------- 0.65; 0.70 and 0.80 ml/kg

Results:

The LD_{50} of α-chloro-N,N-diallylacetamide was found to be 0.70 ml/kg. Survival time was 6 - 48 hours with no striking symptoms of toxicity and with the usual lethargy and loss of appetite.

At autopsy, only pulmonary congestion was of any significant intensity.

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4) Subacute Oral Toxicity in Rats. Sc. Ass # 19524 ; 3/19/56

No. of animals ---------- 20 (10 M and 10 F) 10 controls.
Duration ---------- 30 days 5-day/week feeding.
Route ---------- Oral (stomach tube using corn oil emulsion).
Dosage ---------- 0.37 gm/kg (1/10 of the LD_{50})

Results:

There was an insignificant difference in growth of the animals in favor of the control group. No noticeable differences were noted in food and water consumption between both groups. All animals looked healthy and normal in every respect. No gross or microscopic changes related to drug effect were noted in any of the animals tested. Five animals from both groups were sacrificed for pathological examination.

5) Toxicity by Inhalation in Rats SCAss. 19524

No. of animals ---------- 4 (2 M and 2 F)
Duration ---------- 6 hours
Route ---------- Inhalation (inhalation chamber)

The animals were placed in an inhalation chamber and exposed for 6 hours to an atmosphere containing vapors of the compound, produced by a stream of air at 15 pounds per square inch through an atomizing device. Observations were made for a period of 24 hours.

Results:

Significant signs were observed beginning from the fifth and sixth hours (sniffing and coughing) and at the end of the test displayed heavy, short breathing.

Two of the animals died 18 hours after being removed from the chamber, and two others died in 24 hours.

TEST MATERIALS: "Randox Emulsifiable Concentrate."

6) Acute Oral Toxicity in Rabbits (NR) SA. 01/11/56.

No. of animals ---------- 7 (3 M and 4 F)
Route ---------- Oral (stomach tube)
Dosage ---------- 0.20; 0.25; 0.30; 0.37 and 0.50 gm/kg
Duration ---------- 7 days

Results:

The MLD was placed between 0.25 and 0.30 gm/kg. The animals which died (6) showed decreased activity within one hour of dosage. Death was preceded by collapse and convulsions.

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TEST MATERIAL: "Dilutions of 2-chloro-N, N-diallyl-acetamide"

7) Eye Irritation in Rabbits

No. of animals ---------------- 6 (2 M and 4 F)
Duration ---------------------- 48 hours
Dosage ------------------------ Two dilutions used (4 lbs/18 gal. of water and 4 lbs in 32 gal. of water for each group of 3 animals)

Results: Immediate reactions were observed in all treated animals.

a) 4 lbs in 18 gallons of water dilution: within one hour the pupils of the treated eyes were less than half the diameter of the pupils of the respective controls. This was associated with moderate swelling and reddening of palpebral conjunctivae. The cornea remained clear in all cases.

b) 4 lbs in 32 gallons of water: results were similar to the precedent group but of a lesser degree. Pupil contraction was not so pronounced and no reddening of the palpebral conjunctivae was observed in two of the animals, with a slight reddening in the third. No effect on the cornea was noted.

8) Acute Oral Toxicity in Rats (LD_{50}) SA - 09/17/54

TEST MATERIAL: "Randox (CDAA) Emulsifiable Concentrate for Rats"

No. of animals -------------- 22 (10 M and 12 F)
Route ----------------------- Oral (stomach tube)
Dosage ---------------------- 0.63; 0.73 and 0.83 gm/kg

Results:

LD_{50} for this route was estimated to be 0.75 gram/kg. Majority of deaths occurred in 8 - 24 hours. Two animals survived for 6 days but lost about 20% of their weight. Signs of toxicity included discomfort, lethargy followed by coma. At autopsy, the gastrointestinal tract was moderately irritated, the liver discolored and some pulmonary congestion.

9) Toxicity Study by Skin Absorption in Rabbits.

TEST MATERIAL: "Randox Emulsifiable Concentrate for Rabbits"

No. of animals -------------- 7 (all males)
Duration -------------------- 5 days
Route ----------------------- Skin (clipped with plastic shield)
Dosage ---------------------- Single dose of the undiluted compound. (0.075-0.125; 0.160; 0.20; 0.35 and 0.60 gm/kg)

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Results:

The Minimum Lethal Dose (MLD) was 0.16 to 0.20 gm/kg with survival time ranging from 4 hours to overnite. Some nervous reactions appeared in the animals within 30 minutes following application of the liquid. Four animals (4 to 7) became lethargic and collapsed. Survivors showed normal activity in 2 to 3 days. At autopsy no changes were detected in the viscera.

10) Skin Irritation Study in Rabbits.

No. of animals ---------- 3 (all males)
Duration ---------- 5 days
Route ---------- Skin (intact)
Dosage ---------- Not given (probably the same as the precedent)

TEST MATERIALS:

a) Emulsifiable Concentrate, 43.8% Active.

b) Soluble Concentrate, 46.0% Active.

Results:

Application of the compound to intact skin of rabbits resulted in severe erythema with blistering and moderate eschar formation and edema. Edema decreased in 48 hours. However, erythema remained severe and there was a subcutaneous damage of about 1 - 2 mm. in depth. The condition improved slightly in 5 days. The skin took on a leathery, dark brown appearance, and in approximately 10 days there was evidence of tissue repair around the burned area.

11) Ocular Irritation Study in Rabbits.

No. of animals ---------- 3 (all males)
Duration ---------- 5 days
Route ---------- Ocular (conjunctival sac of right eye; left eye served as a control)
Dosage ---------- (0.1 ml of sample was used)

Results:

The application of the compound caused much pain in the treated animals. Severe erythema and edema and complete closure of the lids and marked discharge were observed in less than 1 hour. Within 24 hours the left eye appeared severely damaged. There was hemorrhage, no reaction to light and the iris was practically invisible. The eye remained shut and swollen with an abnormal discharge for several days after the regular 5 days observation.

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13) Acute Oral Toxicity Studies in Rats (LD_{50}) Younger Lab ; 04/2/59 Y59-9

TEST MATERIAL: Randox - 20 Granular

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No. of animals ---------- 22 (12 M and 10 F)
Route ---------- Oral (stomach tube)
Dosage ---------- 3400; 3750; 3160 and 3630 mg/kg. A 25% aqueous solution-suspension was used.

Results:

The oral LD_{50} was placed at 3250 mg/kg with lower and upper limits of 2990 to 3640 mg/kg.

This is equivalent to an LD_{50} of 650 mg/kg of Randox with lower and upper limits of 578 to 728 mg/kg.

Survival time was several hours to 48 hours with most deaths occurring overnight. Early onset of tremors was followed by weakness, coma and convulsions. At autopsy there was only pulmonary hyperemia.

13) Skin Absorption Study in Rabbits. (MLD) YL # Y59-9; 3/10/59

TEST MATERIAL: Randox Granules 20% (30% aqueous suspension of the powder).

No. of animals ---------- 7 (4 M and 3 F)
Route ---------- Skin (intact)
Dosage ---------- 1000; 1500; 2000; 2500; 3000; 3750 and 500 mg/kg.

Results:

The MLD by skin absorption was greater than 2000 mg/kg and less than 2500 mg/kg. This is equivalent to a range of 400 to 500 mg/kg of Randox. Survival time was 3 - 5 days. Toxic symptoms included poor appetite, tremors, irregular breathing and diarrhea. Two of the animals showed convulsive spasms. At autopsy, pulmonary hyperemia was the principal abnormality noted.

14) Skin Irritation Study in Rabbits # Y59-9; 4/26/59

No. of animals ---------- 3 (sex not given)
Duration ---------- 5 days
Route ---------- Skin (intact). A 30% aqueous suspension was used, and was removed at 24 hours.

Observations were made over a period of several days for irritation.

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Results:

After 1 hour there was a slight edema with slight to well defined erythema. Edema increased to a well defined stage within 4 hours. The inflammation remained substantially the same overnight.

Removal of the compound dropped the irritation to a very slight redness on two of the animals and the third was free of irritation.

15) Eye Irritation Study in Rabbits ~~Y59-4~~ Y59-9; 412159

No. of animals	3
Duration	5 days (120 hours)
Route	Ocular (conjunctival sac of the right eye)
Dosage	20.0 mg of the compound finely ground, and it was washed with saline after 24 hours.

Results:

After 1 hour, mild edema, copious lacrimation, moderate erythema of the palpebral conjunctivae and slight iris congestion were noted. Congestion increased within 4 hours but improved overnight and disappeared by the fifth day.

SUMMARY:

a) Acute and subacute toxicity studies did not show any specific changes and no striking symptoms of toxicity. Acute studies show only pulmonary congestion as an almost constant finding. Subacute studies did not reveal any abnormal deviation of the parameters used, like body weight, mortality, hematological studies, clinical chemistry determinations, Urinalysis, organ weights and Pathological findings.

b) Topical application of the compound showed a moderate irritation of skin and eye in rabbits with the exception of the active concentrate (~9%) which caused severe damage to the eyes of rabbits with permanent loss of sight. This same "concentrate" seems to be very irritant for the skin of rabbits causing severe erythema, edema and eschar formation with blistering of the affected skin.

c) Skin absorption studies in rabbits were done for establishing the "LD50" which was placed between 0.15-0.20 gm/kg with survival time from 4 hours to overnite.

d) Inhalation studies in rats showed toxic symptoms as early as the fifth hour of exposure and all animals were dead by 24 hours.

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e) LD_{50} were as following:

1) In rats (Emulsifiable Concentrate)---------- 0.70 ml/kg.
2) In rats (Emulsifiable Concentrate for Rats) ------- 0.75 gm/kg.
3) In rats (2% - Granular) ---------- 3250 mg/kg.

COMMENTS:

1) The compound seems to be well tolerated by the oral route in dogs and rats. Subacute studies did not show any toxicity symptoms and no abnormalities of laboratory tests or pathological findings.

2) The topical studies on the contrary (skin and eye irritation) show that in general "Randox" has a moderate irritating effect upon these structures with the exception of the "Active concentrate, 48%" which has a very severe irritating action upon the skin and eye of rabbits.

3) The compound seems to be well absorbed by the intact skin of rabbits in which survival time was from 4 hours to overnite, and about 6)-7)% of mortality. Likewise, the compound appears to be very toxic by inhalation in rats in which the mortality was of a 100% in 24 hours after a 6 hour exposure in an inhalation chamber.

4) No significant residue of "a-chloro-N,N-diallylacetamide" (CDAA or Randox) were found in field treated castor beans, potatoes, tomatoes, onions, celery, sugar cane, soybeans, lima beans, snap beans, sorghum, cabbage, sweet potatoes, ornamentals.

The requested negligible tolerance requests for this compound is safe for the above listed crops.

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BVM
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