1-23-78

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: January 23, 1978

SUBJECT: ROZOL Tracking Powder Registration#7173-113
Caswell#211C

FROM: William Dykstra, Ph.D
Toxicology Branch

WRD 1/24/78
E/or WMB 1/26/78

TO: William Miller (11)

Action Type: Extend application for use with Bats

Product Manager: William Miller (11)

Recommendations:

1. The toxicity studies submitted and reviewed do not allow an assessment of the possible hazards associated with long term exposure (especially inhalation) or an assessment of possible effects on reproduction. Without further evidence one must assume that such risks do exist as a result of the particular use pattern (several pounds distributed loosely in attics of residences). We therefore require scientific evidence about the likelihood of human exposure and/or label restriction which reduce the probability of exposure to virtually zero and/or long term inhalation, teratology, and reproduction studies with the active ingredient.

Note to P.M.

The submitted toxicological data has been reviewed and the current concerns regarding the large amounts of powder used in attics, the danger of chronic inhalation of the powder by humans and domestic animals, and the possible exposure to female humans warrant the submission of the additional toxicology studies listed and the label amendment.

Review

1. Toxicity studies on the oxidation products of chlorophacinone (Virginia Polytechnic Institute and State University, R. Ryland E. Webb, 9/13/72; memorandum to F. Horsfall

A. 4-chlorobenzophenone (97%)

Aldrich Chem. Co.

Administered once per orally in Tween 80; corn oil (20:80)

Dose (mg/kg)	Mortality (7 day observations)
800	0/5
100	0/5
10	0/5

B. Phthalic Acid (99%) Aldrich Chem. Co.

Administered once per orally in Tween 80: Corn Oil (20:80)

Dose mg/kg	Mortality (7 day observation)
250	0/5
125	0/5
62:5	0/5

Conclusion: No mortality from these two oxidation products

Classification: Supplementary data
(1) Sex & Species of animals are not identified

2. Complete Results of the Acute Oral Toxicity Test (performed by Lipha, France)

Chlorophacinone was administered on suspension in gum arabic at 10% concentrations. Twelve lots of eight or nine rats were used and the product, in suspension in gum Arabic, is administered at 10% by means of esophogus intubation. Mortality is noted at 2 days, 8 days and 14 days. The results obtained (total mortality) allows us to compute the LD_{50} according to Behrens and Karber method.

Results

LD_{50} = 20.5 mg/kg P.O after 8 and 14 days
Maximum tolerated dose = 1 mg/kg

Classification: Supplementary DATA
(1) Sex of rat not given
(2) No necropsy or toxic signs reported.

3. Results of Toxicity Tests by Inhalation, by Dermal Contact and the local skin tolerance

a. Acute Toxicity by Inhalation

Test Material: 1% solution of Chlorophacinone in polyoxyethylene glycol 300. Density 3 mg/L of air. one hour exposure of 10 male and 10 female rats were used. Observed for 14 days.

Results

No mortality $LC_{50} > 3$ mg/liter

Classification: Core Minimum DATA

TOX Category: III Caution

b. Chlorophacinone Acute Toxicity by Inhalation

A concentration of 2 mg/L (of a 2% chlorophacinone concentrate). 10 micron fineness of Powder. 10 male and 10 females rats were exposed for one hour and observed for 14 days.

Results

No deaths $LC_{50} > 2$ mg/L

Classification: Core Minimum DATA

TOX Category: III Caution

C. Chlorophacinone: Acute Dermal Toxicity of Technical Powder

4 albino rabbits weighing 2.5 kg each were used. Skin was depilated by shears. Two grams (2 gms) of fine powder (10μ) was applied to an area 1 inch by 1 inch. The product was maintained in place by compressed surgical adhesive tape on all 4 sides. The rabbits were kept for 24 hours, in an immobilization box to avoid their pulling the tape off and their absorbing the product. After this period of time and after the compress was removed, the animals were carefully washed with soap and water to eliminate the product that could have been licked.

Results

All 4 rabbits died $LD_{50} > 0.8$ gm/kg

Classification: Inadequate Study

a. LD_{50} has not been determined

b. Only one dose level given

c. Sex of rabbits not given

d. Possibly TOX Cat. II: WARNING

D. Local Tolerance on Albino Rabbit Back Skin

Six (6) albino male rabbits, 24-2.6 kg, were subjected to a careful depilution of the loin area. 1 inch square gauze pad, impregnated with 500 mg of LM 91 in solution (incomplete), is applied to the right side and 2 ml of acetone is applied to the left side. Rabbits kept for 24 hours. Skin is then washed and observation at 24, 48 and 72 hours.

Note: LM 91 is code name for Chlorophacinone

Results: At 72 hours Treated Side

Rabbit 1 - purple colorations, almost black, inflammation
Rabbit 2 - similar to 1
Rabbit 3 - eschar
Rabbit 4 - black eschar
Rabbit 5 - skin hardened, eschar
Rabbit 6 - skin inflammed, eschar

Mortality: All rabbits died within 3 weeks

Classification: Core-Minimum DATA

TOX Category: I DANGER

4. Toxicity in Domestic Animals

The Toxicity studies were carried out with hens (Lipha, Lyon) pigs, dogs and cats (Veterinary School, Lyon).

The object of these tests was to compare the actual toxicity of chlorophacinone and warfarine in the concentrations in which these substances are used on grain, i.e.,

0.005% for chlorophacinone
0.025% for warfarine

a. Toxicity of Chlorophacinone in Hens

Hens in individual cages were fed as follows for 15 days:

- three with grain containing 0.025% WAR.
- three with grain containing 0.005% Chlorop.

After 15 days, normal food was given.

Results

Mortality

warfarine	2/3 on the 13th & 20th day
chlorophacinone	2/3 on the 10th & 16 day
control	0/3

Conclusion: Chlorophacinone has appreciably the same toxicity as warfarine.

Classification: Supplementary DATA

b. I. Toxicity in Pigs: A comparison of Chlorophacinone and Warfarine.

Three groups (9 piglets - castrated and weighing 30 Kg) were used

Group A - Control groups received totaliment (B 30/40) food at rate of 2 kg per day.

Group B - Received every day for 15 days, the same food, with the addition of the quantity of warfarine present in 20 gm of grain at 0.025% concentration.

Group C - Received every day for 15 days, the same food, with the addition of the chlorophacinone present in 20 gm grain at 0.005% concentration.

Results:	Mortality	
Group B	3/3	Day 21, 22 (2) one pig sacrificed for necropsy
Group C	0/3	
Group A	0/3	

Necropsy

Warfarin treated Pigs (Group B) - Corpse pale, jaindiced, liver congested, hemorrhage in abdomen, kidneys hemorrhagic spots.

Chlorophacinone treated Pigs (Group C) - Slaughtered to compare to Group B. There was no injury worthy of note. The blood clotted less quickly than normal.

Control (Group A) - Normal appearance and normal clotting times.

Conclusion: In pigs, chlorophacinone is much less toxic than warfarine.

Classification: Supplementary DATA

b. II. Acute Toxicity Tests - Pigs

(1) First Test

One of the pigs which had served as a control in the preceding experiment was fed, during 5 days with a daily ration of 2 Kg food with the addition of 1 Kg of corn containing 0.005% chlorophacinone.

Result: Mortality on day 7.

Necropsy: Abdomen full of unclotted blood.

(2) Second Test

A second pig, which had served as a Group A (reference pig) in the semi-chronic toxicity experiments, received every day for 5 days, a ration of 2 Kg food with the addition of 250 gm of corn at 0.005% chlorophacinone (12.5 mg of pure chlorophacinone per day).

Results: First clinical signs appeared on the 17th day after beginning of intoxication. Skin reddened, pig showed fatigue, excreta was soft. Clothing time was less than normal. Pig then regained weight. 4 months later, the pig survived.

Conclusion: Pigs are able to tolerate small amounts of daily consumption of chlorophacinone.

Classification: Supplementary DATA

C. Toxicity of Chlorophacinone in Dogs

Two dogs, a female hound (B) and a male griffon (G), aged 3 and 4 years respectively, and weighing almost 10 Kg each; well accustomed to the food and to the place (food: cooked beef, bread soup with "pasta") received in their food every day for 10 days, the amount of chlorophacinone present in 10 gm. of grain at 0.005% concentration (i.e., 0.5 mg of pure chlorophacinone per day).

Results: Dog B - Death on 11th day
Dog G - Progress toward a cure

Conclusion: One dog died and one survived.

Classification: Inadequate DATA

D. Toxicity of chlorophacinone in cats

Three cats were used in this investigation

	Weight
- a ginger cat (CI)	2.45 Kg
- a black she - cat (CII)	2.3 Kg
- a grey cat (CIII)	2.4 Kg

Each animal received every day for ten days in its daily ration of food, the quantity of chlorophacinone present in 2 gm of grain at 0.005% (i.e., 1 mg of pure chlorophacinone).

Results

The black cat (C2) deteriorated rapidly from the ninth day of intoxication. It weakened, its gums bled and its temperature droped to 35 °C. Death on 18th day.

The two other cats survived after showing on the tenth day of intoxication symptoms of intense anemia; sleeplessness, difficult breathing.

Conclusion: Chlorophacinone is toxic to cats.

Classification: Inadequate DATA

5. Chlorophacinone in Humans

The effect of the absorption of a single dose of 20 mg of Chlorophacinone on the prothrombin - rating od three patients.

Day	Progress of Exp.	Patients A	B	C
	Normal Pro-Time After	105%	100%	90%
1	20 mg of Chloroph.	65	95	70
2	Pro-Time	35	48	38
3		38	42	46
4		40	34	51
5		37	45	56
6		60	53	70
7		65	70	85
8		80	100	90

Conclusions - The three patients, A, B, and C, each having absorbed a single dose of 20 mg of Chlorophacinone did not have a Pro-Time below 35, 34 and 38%, respectively.

In cases of pathological thrombasis, when the amount of prothrombin is, e.g., 15% to 30%, the condition is regarded as being capable of therapeutic treatment. If a person consumes 400 gm of rodenticidal bait containing 0.005% of Chlorophacinone, i.e., 20 mg of the substance, his prothrcombin drops to 35%, a figure which is not yet dangerous.

Classification: Supplementary Data

6. Warfarine in Humans

Day		Patient D	E	F	G	H
0	Pro-time	80	100	90	95	100
After Warfarin		80 mg	60 mg	60 mg	70 mg	120 mg
1	Pro-time	46	54	43	51	58
2		15	20	11	15	9
3		0	5	0	0	0

After 50 mg VitK$_1$

4 Pro-time	20	30	28	22	30
5 Pro-time	50	45	52	48	55
6 Pro-time	55	65	60	70	63

Conclusion: The average dangerous dose for the 5 cases was therefore 78 mg. The protheombin ratings increased after intravenous injection of 50 mg of Vit. K$_1$. A comparison of the two tables shows that absorption of 20 mg of chlorophacinone does not bring the prothrombin rating into the danger zone; whereas the absorption of 78 mg of warfarine (on average) lowers the prothrombin rating to zero (blood incoagulable). In the rodenticidal baits containing 0.025% of warfarine, 78 mg are present in 312 gm of bait. Withbaits containing 0.005% chlorophacinone, 20 mg of chlorophacinone are present in 400 gm of bait.

It follows that 400 gm of chlorophacinone - based bait does not render the blood incoagulable but 312 gm of warfarine-based bait does render the blood incoagulable.

7. Eye Irritation Test Chlorophacinone oil concentrate

Test Material: 0.25% chlorophacinone oil

4 female rabbits of common gray strain weighing 2.5-2.7 Kg, received 1.5 ml in the left eye and the right eye served as a control. Observations at 24, 48, 72 hours and 7 days.

Results: A comparison of the eyes at 72 hours showed no difference between control and treated eyes.

Classification: Core-Minimum Data

TOX Category: IV Caution

8. Effect of one application of liquid concentrate on the rabbit skin on the lowering of the prothrombin level.

Method: Tests made on 5 male rabbits, common strain, weighing an average of 2.5 kilos each. The back of the rabbits was shaved. Rest of 4 hours and wash a 100 Cm^2 surface on the back with the 0.25% oil of concentrate on the rabbits the rabbits are maintained with test material for 4 hours and then the backs are carefully washed to eliminate the product.

Results: During the test, 2 control animals have not been subjected to treatment.

Lot	No. Rabbits	DAYS Number with low Pro-time 1st day	2nd day	3rd day
Control	2	0	0	0
oil of concentrate	5	1	3	1

Experiments have noted every day the number of rabbits which prothrombin rate reached a level between 40% and 15% of the initial prothrombin level.

Conclusions: The prothrombin level in the rabbits treated by contact of the liquid concentrate has been lowered. Therefore there is a skin absorption of the product.

Classification: Supplementary Data

9. Acute Dermal Toxicity test performed with Chlorophacinone oil concentrate at different levels (by Lipha, France.)

This test was performed on three lots of 5 male rabbits weighing 2.5 Kg each.

The chlorophacinone oil concentrate was applied on the shaved back skin of the rabbit and left for a period over 24 hours. The area treated covered 100 Cm^2. Animals were washed at the end of the test. Mortality by hemorrhage was noted in the following 10 days.

1st lot - treated with a .25% oil
2nd lot - treated with a .375% oil
3rd lot - treated with a .552% oil

Results

Dermal LD_{50} = .40% concentrate

Classification: Supplementary Data

10. Chlorophacinone: Sub-acute Dermal and Inhalation Toxicity.

a). Purpose is to determine the maximum tolerated dosage by dermal application on albino rabbits.

Three lots of 4 rabbits of an average weight of 2 Kg. Entire back has been shaved. Applied on the lumbar region, over an area representing approximately 15% of the entire body surface, the product dissolved in 3 ml of polyoxyethylene glycol 300. Penetration through the skin was excellent.

After 6 hours of exposure, the region was washed. 15 applications were made during the next three weeks.

Dosages Administered

Weak dosage - 4 rabbits - 15 micrograms/kg/day
Medium dosage - 4 rabbits - 150 " " "
Strong dosage - 4 rabbits - 1500 " " "

Results

Weak dosage - No effect - no mortality

Medium dosage - 3 out of 4 died, Thoracic hemorrhage

Strong dosgae - 4 out of 4 died Thoracic hemorrhage

Conclusion: The maximum tolerated dose was established at 15 microgram/kg/day in this study.

Classification: Supplementary Data

b. Acute toxicity by Inhalation

Purpose is to determine the acute toxicity on rats by inhalation of of a 1% solution of chlorophacinone in polyoxyethylene glycol 300. Density of air is 3 mg/Liter.

10 male rats and 10 female rats were exposed for one hour then observed for 14 days.

Results: No mortality $LC_{50} > 3$ mg/L

Classification: Core-Minimum Data

TOX Category: III Caution

Type By: TH