UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 17 1989

007615

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Strychnine Alkaloid

HED Project No.: 9-2059
TOX Chem No.: 805

FROM: Ray Landolt 10/30/89
Review Section I
Toxicology Branch II - Herbicide, Fungicide, and Antimicrobial Support
Health Effects Division (H7509C)

TO: Steve Palmateer, PM 16
Insecticide-Rodenticide Support
Registration Division (H7505C)

THRU: Mike Ioannou, Section Head J M Ioannou 11/7/89
Review Section I
Toxicology Branch II - Herbicide, Fungicide, and Antimicrobial Support
Health Effects Division (H7509C)

and

Marcia van Gemert, Chief Marcia Gemert 11/9/89
Toxicology Branch II - Herbicide, Fungicide, and Antimicrobial Support
Health Effects Division (H7509C)

Registrant: Wyoming Department of Agriculture, Letter of August 15, 1989

Action Requested

In response to the deficiencies cited in the review by R. Landolt, February 17, 1989 (copy attached) of the acute toxicity studies, the registrant has submitted the following revised reports.

007615

Study	Material	Original Report MRID No.	Revised Report MRID No.
Acute Oral Toxicity	99.42%	409089-01	412107-01
Acute Dermal Toxicity	99.42%	409089-02	412107-02
Primary Dermal Irritation	99.42%	409089-03	412107-03
Primary Eye Irritation	99.42%	409089-04	412107-04
Acute Oral Toxicity (Egg Bait)	35.4 mg/egg	409089-05	412107-05

Conclusions:

1. The purity of the technical material in these acute toxicity studies was reported to be 99.42%.

2. Acute Oral Toxicity Study

   a. Deficiencies

      1) The volume administered (mL/100 g body weight) was not reported.

         Response - The revised report was corrected to show that the volume of the test material administered (mL/100 g body weight) ranged from 0.25 to 0.37 for males and 0.08 to 0.12 for females

      2) The typical signs of central nervous system stimulation, i.e., tonic convulsions, were not reported in this study for strychnine.

         Response - "The typical signs of central nervous system stimulation for strychnine, i.e., tonic convulsions, were not observed during this study, but may have occurred as cyclical events when the animals were not being observed."

         Reviewer's Comment - It is apparent that these animals were observed at the one hour interval rather than during the first hour following administration of the test material. Or the signs of central nervous system stimulation were not recognized when they occurred.

   b. Results:

      LD_{50} - Males 6.4 (5.8-7.1) mg/kg
      Females 2.2 (1.9-2.5) mg/kg

c. Conclusions

Classification of Data - From Supplementary to Minimum.

1) Deficiency - Signs of toxicity were not recorded during the first hour following administration of the test material.

2) Toxicity Category I

3. Acute Dermal Toxicity Study

a. Deficiencies

1) The application of a white powder via a syringe-type applicator must be clarified.

Response - The reference to a syringe-type applicator was omitted from the report.

2) The test substance (white powder) was not moistened with water or suitable vehicle.

Response - "Moistened with distilled water" was added to the revised report.

b. Results

LD_{50} > 2.0 g/kg (bwt).

c. Conclusions

Classification of Data - From Supplementary to Guideline.

Toxicity Category III

4. Primary Dermal Irritation

a. Deficiency

- Purity of the technical material was not reported.

Response - The purity of Lot No. R/11/85 was reported to be 99.42%.

b. Results

No irritation or mortality were reported.

c. Conclusions

Classification of Data - From Supplementary to Guideline.

Toxicity Category IV

5. Primary Eye Irritation

a. Deficiencies

1) The use of a syringe-type applicator to administer a volume of 0.1 mL equivalent dose of a white powder should be clarified.

Response - "A 1.0 ml syringe was modified by removing the tip to provide a dose of 0.1 ml equivalent. The average weight of ten, 0.1 ml equivalent doses, using the applicator, was determined to be 52 mg."

Reviewer's Comment - Strychnine is highly toxic by the ocular route of exposure. With 4/6 animals dead within 48 hours from the application of a 52 mg dose to the rabbit eye, the approximate lethal dose of 40 mg/kg reported in the results of the attached Data Evaluation Report is incorrect and should read 20.8 mg/ kg based on the weight of a 2.5 kg animal.

2) The time of onset and duration of signs of toxicity were not reported.

Response - Within 1 hour of compound administration, tremors and ataxia were reported. Following the 1-hour observation, 3/6 rabbits died within 24 hours and 1/6 died within 48 hours. At the 24-hour observation, ataxia, loss of hind limb mobility and reflex were reported for the surviving rabbits. One rabbit exhibited a yellow nasal discharge and prostration during the 48- and 72-hour observation periods.

b. Results

Within 48 hours, 4/6 animals were dead with slight irritation reported for the two survivors.

c. Conclusions

Classification of Data - From Supplementary to Guideline.

Toxicity Category III for eye irritation.
Toxicity Category I for systemic toxicity.

6. Acute Oral Toxicity

a. Deficiencies

1) The percent concentration of the egg bait, the concentration of the dosing solution (mg/mL), and the volume administered (mL/100 g body weight) were not reported.

Response - "Since the actual use will be with eggs of slightly different volumes, the results reported will be somewhat variable in the field. The concentration of the active ingredient used in this study was 0.56 mg/ml. However, the LD_{50} calculated in this study was based on the complete egg bait preparation which had a specific gravity of 1.02 g/ml."

The volume of the test material administered ranged from 0.49 to 0.96 mL/100 g body weight.

Reviewer's Comment - Per telephone call of October 18, 1989 to Steve Palmateer (PM 16), each strychnine-treated egg bait will contain approximately 35.4 mg of strychnine alkaloid.

2) The typical signs of central nervous system stimulation, i.e., tonic convulsions, were not reported in this study for strychnine.

Response - "The typical signs of central nervous system stimulation for strychnine, i.e., tonic convulsions, were not observed during the study but may have occurred as cyclical events when the animals were not being observed."

Reviewer's Comment - It is apparent that these animals were observed at the one hour interval rather than during the first hour following administration of the test material. Or the signs of central nervous system stimulation were not recognized when they occurred.

3) An observation coded 2 was not identified.

Response - "2 = anogenital area soiled."

b. Results

LD_{50} - Males > 9.8 g/kg
Females - 6.6 g/kg (5.4 to 8.0) g/kg

c. Conclusions

Classification of Data - From Supplemental to Minimum.

o Deficiency - Signs of toxicity were not recorded during the first hour following administration of the test material.

Toxicity Category IV

Reviewer's Comment - Toxicity Category IV labeling does not represent the hazard associated with the use of strychnine egg baits. The registrant is not relieved of labeling each strychnine-treated bait with the word "Poison" in three locations on the egg (Exemption for Use of Strychnine to Control Rabid Skunks, FEDERAL REGISTER 50 No. 229, November 27, 1985).

Attachment

Tox Chem. No. 805-Strychnine File Last Updated 10/02/89

Citation	Material	EPA Accession/ MRID No.	Results:	Toxicity Category	CORE Grade/ Doc. No.
Acute Oral LD_{50}; Species: Rat; MB Res Lab for WY Dept. of Agric. 88-9166A; September 14, 1988	Egg Bait 35.4 mg/ egg	409089-05	LD_{50} (M) = 9.8 g/kg, LD_{50} (F) = 6.6 (5.4-8.0) g/kg. Death occurred within 1 hour for males without signs of toxicity reported. Tremors were observed in females within 1 to 4 hours. Males and females were observed to be hyperactive upon manipulation.	IV	Supplementary 007035 Minimum
Acute Oral LD_{50}; Species: Rat; MB Res Lab for WY Dept. of Agric. 88-9165A; September 20, 1988	Tech 99.42%	409089-01 412107-01	LD_{50} (M) = 6.4 (5.8-7.1) LD_{50} (F) = 2.2 (1.9-2.5) mg/kg Death occurred within 1 hour. Signs of toxicity: piloerection, tremors, tachypnea, lethargy, dyspnea, and prostration were observed within 1 hour.	I	Supplementary 007035 Minimum
Acute Dermal LD_{50}; Species: Rabbit; MB Res Lab for WY Dept. of Agric. 88-9165B; September 21, 1988	Tech 99.42%	409089-02 412107-02	LD_{50} > 2.0 g/kg. No signs of toxicity observed.	III	Supplementary 007035 Guideline
Primary Dermal Irritation; Species: Rabbit; MB Res Lab for WY Dept. of Agric. 88-9165C; September 2, 1988	Tech 99.42%	409089-03 412107-03	No irritation, mortality, or signs of toxicity were observed.	IV	Supplementary 007035 Guideline

ox Chem. No. 805-Strychnine File Last Updated 10/02/89

Citation	Material	EPA Accession/ MRID No.	Results:	Toxicity Category	CORE Grade/ Doc. No.
rimary Eye Irritation; pecies: Rabbit; Res Lab for WY Dept. of Agric. 88-9165D; ly 22, 1988	Tech 99.42%	409089-04 412107-04	Mortality of 4/6 animals with slight irritation in two survivors, clearing in one by 48 hours and present at 72 hours in the other survivor. Toxicity Category I for systemic toxicity. Toxicity Category III for eye irritation.	III	Supplementary 007035 Guideline

007615

REVIEWER

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

007035

FEB 17 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Strychnine Alkaloid

HED Project No.: 9-0562
TOX Chem No.: 805

FROM: Ray Landolt 2/9/89
Review Section I
Toxicology Branch II - Herbicide, Fungicide, and Antimicrobial Support
Health Effects Division (TS-769C)

TO: William H. Miller, PM 16
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Mike Ioannou, Acting Section Head M Ioannou 2/13/89
Review Section I
Toxicology Branch II - Herbicide, Fungicide, and Antimicrobial Support
Health Effects Division (TS-769C)

and

Marcia van Gemert, Acting Chief Marcia van Gemert 2/15/89
Toxicology Branch II - Herbicide, Fungicide, and Antimicrobial Support
Health Effects Division (TS-769C)

Registrant: Wyoming Department of Agriculture, letter of November 18, 1988.

Action Requested

Review the following acute toxicity studies submitted in support of the registration of strychnine alkaloid in an egg bait (EPA Registration No. 35978-7) for control of rabid skunks.

Study	Material	MRID No.
Acute Oral Toxicity - Rat	Technical	409089-01
Acute Dermal Toxicity - Rabbit	Technical	409089-02

Study	Material	MRID No.
Primary Dermal Irritation - Rabbit	Technical	409089-03
Primary Eye Irritation - Rabbit	Technical	409089-04
Acute Oral Toxicity - Rat	Egg Bait	409089-05

Recommendation

These studies are not acceptable. The deficiencies are cited in the review of each study.

Reviewed By: Ray Landolt 2/9/89
Section I, Toxicology Branch - HFAS (TS-769C)
Secondary Reviewer: James Rowe 2/13/89
Section I, Toxicology Branch - HFAS (TS-769C)

DATA EVALUATION REPORT

Study Type: Acute Oral Toxicity - Rat (81-1)

TOX Chem No.: 805
MRID No.: 409089-01

Test Material: Strychnine Alkaloid - Technical
A white powder administered as a 0.2% mixture in distilled water

Study ID: MB 88-9165A

Sponsor: Wyoming Department of Agriculture

Testing Facility: MB Research Laboratories, Inc.
Spinnerstown, PA

Title of Report: Oral Toxicity in Albino Rats.

Authors: Daniel R. Cerven

Report Issued September 20, 1988

Animals:

Eight-week-old Wistar Albino rats weighing between 204 to 300 g for males and 217 to 288 g for females were supplied by Ace Animals. The animals were housed 5/sex/cage and fasted 16-20 hours prior to dosing.

Method:

Five groups of five male rats/group were dosed by gavage at 4.9, 5.5, 5.8, 6.6, and 7.3 mg/kg. Four groups of five female rats/group were dosed by gavage at 1.5, 1.9, 2.1, and 2.4 mg/kg. The animals were observed at 1, 2, and 4 hours then twice daily for 14 days. Body weights were recorded initially, and on day 7 and 14 of the study. All animals were examined for gross pathology.

Results: LD_{50}, males 6.4 (5.8 - 7.1) mg/kg
females 2.2 (1.9 - 2.5) mg/kg

No deaths were reported for the lowest dosage level in males (4.9 mg/kg) or in females (1.5 mg/kg). Deaths at the higher dosage levels occurred within 1 hour of compound administration. Signs of toxicity observed within the first hour are piloerection, dyspnea, lethargy and prostration in males and tachypnea, tremors and piloerection in female rats. Tonic convulsions, characteristic of strychnine toxicity, were not reported.

Gross necropsy observations of those animals that died within 1 hour of compound administration consisted of lungs and liver moderately dark in appearance with the heart moderately dilated.

Conclusions:

1. Classification of Data - Supplementary

   A. Deficiency:

      i. Purity of the technical material was not reported.

      ii. The volume administered (mL/100 g body weight) was not reported.

      iii. The typical signs of central nervous system stimulation, i.e., tonic convulsions were not reported in this study for strychnine.

2. Toxicity Category was not determined.

Reviewed By: Ray Landolt 2/9/89
Section I, Toxicology Branch - HFAS (TS-769C)
Secondary Reviewer: James Rowe J.M.R. 2/13/89
Section I, Toxicology Branch - HFAS (TS-769C)

007615
007035

DATA EVALUATION REPORT

Study Type: Acute Dermal Toxicity - Rabbit (81-2)

TOX Chem No.: 805
MRID No.: 409089-02

Test Material: Strychnine Alkaloid - Technical, a white powder

Study ID: MB 88-9165B

Sponsor: Wyoming Department of Agriculture

Testing Facility: MB Research Laboratories, Inc.
Spinnerstown, PA

Title of Report: Acute Dermal Toxicity in Albino Rabbits.

Author: Daniel R. Cerven

Report Issued: October 21, 1988

Animals:

Eight-week-old New Zealand Albino rabbits weighing between 2.3 to 2.6 kg for males and 2.1 to 2.8 kg for females were supplied by Ace Animals. The rabbits were housed individually and fitted with an Elizabethan collar for the duration of the study.

Method:

A white powder was applied "by a syringe type applicator at a dose level of 2.0 g/kg" to the shaven intact dorsal area of 5 male and 5 female rabbits. "The test article was covered with a gauze patch and gentle pressure was applied to the gauze to aid the distribution of the test article over the prepared site. The torso was wrapped with plastic which was secured with nonirritating tape". After 24 hours, the patches were removed, the site was washed gently with water and the test sites were scored (Draize) for dermal irritation at 24 hours, then on days 7 and 14. All animals were observed for signs of toxicity at 1, 2, and 4 hours, then twice daily for 14 days. Body weights were recorded initially, and on day 7 and 14 of the study. All animals were examined for gross pathology.

Results: LD_{50} > 2.0 g/kg (b.wt.)

No erythema or edema were observed. Body weights of the male and female rabbits at the 7- and 14-day intervals were comparable to their initial body weights. No signs of toxicity or gross pathological findings were reported relative to the administration of the test material. One female rabbit exhibited a yellow nasal discharge, lost weight and was found dead on day 9. Gross necropsy findings for this animal were: congested lungs, pale liver, and intestines distended with gas. The death of this animal did not appear related to the application of the test material; but rather a respiratory infection.

Conclusions:

1. Classification of Data - Supplementary

   A. Deficiency:

      i. Purity of the technical material was not reported.

      ii. The application of a white powder via syringe type applicator must be clarified.

      iii. The test substance (white powder) was not moistened with water or suitable vehicle.

2. Toxicity Category was not determined.

007615

Reviewed By: Ray Landolt 2/9/89
Section I, Toxicology Branch - HFAS (TS-769C)
Secondary Reviewer: James Rowe J.M.R. 2/13/89
Section I, Toxicology Branch - HFAS (TS-769C)

007035

DATA EVALUATION REPORT

Study Type: Primary Dermal Irritation (81-5)

TOX Chem No.: 805
MRID No.: 409089-03

Test Material: Strychnine alkaloid - Technical, a white powder

Study ID: MB 88-9165C

Sponsor: Wyoming Department of Agriculture

Testing Facility: MB Research Laboratories, Inc.
Spinnerstown, PA

Title of Report: Primary Dermal Irritation in Albino Rabbits.

Authors: Daniel R. Cerven

Report Issued: September 2, 1988

Animals:

Six, 8-week-old New Zealand Albino rabbits weighing between 2.0 to 3.0 kg were supplied by Sgarlatt's Rabbitry. The animals were housed individually.

Method:

The test material (0.5 g) was moistened with distilled water and applied to the shaven intact skin of each rabbit. The test area (6 cm^2) was covered with a patch, secured with a semi-occlusive dressing and taped. After 4 hours, the wrappings were removed, the test site was washed and scored (Draize) for irritation. Skin reactions were recorded at 30 to 60 minutes, then at 24, 48, and 72 hours.

Results:

No irritation or mortality was reported.

Conclusions:

1. Classification of Data - Supplementary

   A. Deficiency:

      i. Purity of the technical material was not reported.

2. Toxicity Category was not determined.

Reviewed By: Ray Landolt 2/9/89
Section I, Toxicology Branch - HFAS (TS-769C)
Secondary Reviewer: James Rowe 2/13/89
Section I, Toxicology Branch - HFAS (TS-769C)

007615

007035

DATA EVALUATION REPORT

Study Type: Primary Eye Irritation (81-4)

TOX Chem No.: 805
MRID No.: 409089-04

Test Material: Strychnine alkaloid - Technical, a white powder

Study ID: MB 88-9165D

Sponsor: Wyoming Department of Agriculture

Testing Facility: M.B. Research Laboratories, Inc.
Spinnerstown, PA

Title of Report: Eye Irritation in Albino Rabbits.

Authors: Daniel R. Cerven

Report Issued: July 22, 1988

Animals:

Six, 8-week-old New Zealand Albino rabbits weighing between 2.0 to 3.0 kg were supplied by Ace Animals. The rabbits were housed individually.

Methods:

A white powder (0.1 mL equivalent) "was placed by syringe or syringe-type applicator into the conjunctival sac" of one eye of each rabbit. The treated eye of each rabbit was examined for irritation (Draize) at 1 hour postdosing then at 24, 48, and 72 hours. The eyes of all rabbits were examined with sodium fluorescein at 24 hours. All eye were washed following the 24-hour reading.

Results:

Evidence of the test material in the conjunctiva was reported for all six rabbits at the 1-hour observation. Following the 1-hour observation, 3/6 rabbits died within 24-hours and 1/6 died within 48-hours of dosing from an approximate dose of 40 mg/kg. The time from dosing to death was not reported. However, tremors, ataxia, convulsions, and loss of hind limb mobility were reported for all six rabbits. A negative righting reflex, yellow nasal discharge, lethargy, and prostration were reported for the two surviving rabbits. The time of onset and duration of these signs of toxicity were not reported.

One of the surviving rabbits exhibited slight irritation at 1, 24, 48, and 72 hours accompanied by iritis at 24-hours, clearing by the 48-hour observation. Slight irritation was observed in the eye of the other surviving rabbit at 1-hour, clearing by the 48-hour observation.

Conclusions:

1. Classification of Data - Supplementary

   A. Deficiency:

      i. Purity of the technical material was not reported.

      ii. The use of a syringe-type of applicator to administer a volume of 0.1 mL equivalent dose of a white powder should be clarified.

      iii. The time of onset and duration of signs of toxicity were not reported.

2. Toxicity Category was not determined.

17

Reviewed By: Ray Landolt 2/9/89
Section I, Toxicology Branch - HFAS (TS-769C)
Secondary Reviewer: James Rowe J.M.R. 2/13/89
Section I, Toxicology Branch - HFAS (TS-769C)

007615

66,035

DATA EVALUATION REPORT

Study Type: Acute Oral Toxicity (81-1)

TOX Chem No.: 805
MRID No.: 409089-05

Test Material: Strychnine alkaloid in an egg bait

Study ID: MB 88-9166A

Sponsor: Wyoming Department of Agriculture

Testing Facility: MB Research Laboratories, Inc.
Spinnerstown, PA

Title of Report: Strychnine Alkaloid Egg Baits.

Wyoming Department of Agriculture has submitted this study in support of the use of strychnine alkaloid injected in an egg bait for control rabid skunks.

Authors: Daniel N. Cerven

Report Issued: September 14, 1988

Animals:

Ten, 8-week-old Wistar Albino rats weighing between 204 to 295 g for five males and 200 to 290 g for five female rats were supplied by Ace Animals. The animals were housed 5/sex/cage ~~and~~ and fasted 16-20 hours prior to dosing.

Preparation of the Test Material:

The test material, 3.54 g of white powder, was added to 10.0 g of Glacial Acetate Acid diluted with "15.46 g of distilled water and 1.0 g of green food coloring" (added as an indicator). "1.0 mL of the test article solution was mixed with the raw eggs to a total volume of 60 mL and dosed from a stir plate."

Method:

Five groups of five female and five male rats per group were dosed by gavage at 5.0, 6.3, 7.8, 8.8, and 9.8 g/kg. Body weights were recorded initially, on day 7, at death, and on day 14 of the study. All animals were observed at 1, 2, and 4 hours then twice daily for 14 days. All animals dying during the study and those terminated after 14 days were subjected to a gross necropsy.

Results:

LD_{50}. males > 9.8 g/kg
females = 6.6 (5.4-8.0) g/kg

Mortality (From this report)

Dose Level g/kg	No. Treated M/F	No. Dead M/F	Day of Death (M/F) 0
5.0	5/5	0/2	0/2
6.3	5/5	1/2	1/2
7.8	5/5	1/2	1/2
8.8	5/5	0/3	0/3
9.8	5/5	0/5	0/5

Observations:

Death of the two males dosed at 6.3 and 7.8 mg/kg occurred within 1 hour of dosing without signs of toxicity report preceding death. Tremors were observed in female rats within 1 to 2 hours following the administration of the test material. Death of the female rats occurred within 1 to 4 hours of compound administration. Males and females were observed to be "hyperactive upon manipulation" within 1 to 4 hours of compound administration. An observation coded 2 was not identified.

One male rat dosed at 9.8 g/kg appeared lethargic during the 2- to 4-hour observation period following compound administration. Typical signs of strychnine toxicity, i.e., tonic convulsions, were not reported in this study.

Necropsy:

Gross necropsy observations of those animals that died within 4 hours of compound administration consisted of congested and hemorrhagic lungs, the liver moderately dark in appearance with the heart slight to moderately dilated.

Conclusion:

1. Classification of Data - Supplementary

   A. Deficiency:

      1. Purity of the technical material was not reported.

19

ii. The percent concentration of the egg bait, the concentration of the dosing solution (mg/mL) and the volume administered (mL/100 g body weight) were not reported.

iii. The typical signs of central nervous system stimulation, i.e., tonic convulsions, were not reported in this study for strychnine.

iv. An observation coded 2 was not identified.

2. Toxicity Category was not deteermined.

END