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

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

MAR 16 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Franklin Gee, Product Manager #17
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 3/16/83
OEP 3/16/83

SUBJECT: (1) A Food Additive Petition (3H5383) for Cyano(3-phenoxyphenyl) methyl 4-chloro-alpha-(1-methylethyl) benzeneacetate (a.k.a. fenvalerate).

(2) Review of Five Acute Toxicity Studies in Support of Evercide® Space and Contact Spray F-2370. (EPA File No. 1021-RLEL) and Evercide® Residual Spray F-2371 (EPA File No. 1021-RLEA).

TOX Chem No. 77A

The McLaughlin Gormley King Company has submitted a food additive petition for the subject chemical (fenvalerate) from the use of Evercide® Space and Contact Spray and Evercide® Residual Spray. The formulated products are to be used to control insects in food service establishments, food manufacturing, and processing establishments, and food warehousing establishments.

The proposed tolerance for fenvalerate (all ~~uses~~ Foods) is 0.05 ppm.

The statement of formula for Evercide® Space and Contact Spray F-2370 (EPA File No. 1021-RLEL) is as follows:

.40% Pyrethrins
.70% Piperonyl butoxide
.70% MGK-264
.05% Fenvalerate

CBI removed

The statement of formula for the Evercide® Residual Spray F-2371 (EPA File No. 1021-RLEA) is as follows:

.050% Pyrethrins
.100% Piperonyl butoxide
.167% MGK-264
.200% Fenvalerate

CBI Removed

CFR 180.[illegible]9 Pydr[illegible] 3/3/83

File last updated 3/3/83

DRAFT

[illegible]0/359

ACCEPTABLE DAILY INTAKE DATA

RAT, Older NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
12.500	250.00	100	0.1250	7.5000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cottonseed (oil)(41)	0.[illegible]00	0.15	0.[illegible]0045
Peanuts(115)	0.020	0.36	0.00011
Potatoes(127)	0.[illegible]20	5.43	0.00163
Soybeans (oil)(148)	0.050	0.92	0.00069
Cabbage,sauerkraut(22)	10.[illegible]00	0.74	0.11037
Pecans(118)	0.200	0.03	0.00009
Cantaloupe(23)	1.000	0.52	0.00782
Honeydewmelons(71)	1.000	0.03	0.00045
Pumpkin,inc squash(131)	1.000	0.11	0.00169
Watermelon(169)	1.000	1.43	0.02146
Muskmelons(98)	1.000	0.03	0.00045
Pears(116)	2.000	0.26	0.00766
Apples(2)	2.000	2.53	0.07590
Cucumbers,inc pickl(46)	0.500	0.73	0.00544
Tomatoes(163)	1.[illegible]00	2.87	0.[illegible]4312
Summer Squash(155)	0.500	0.03	0.00023
Milk&Dairy Products(93)	0.[illegible]00	28.62	0.[illegible]4292
Cattle(26)	1.000	7.18	0.10777
Goats(62)	1.000	0.03	0.00045
Hogs(69)	1.000	3.43	0.05151
Horses(208)	1.[illegible]00	0.03	0.00045
Sheep(145)	1.000	0.19	0.00291
Cauliflower(27)	0.500	0.07	0.00054
Broccoli(19)	2.000	0.10	0.00307
Beans,dry edible(10)	0.250	0.31	0.00116
Corn,grain(68)	0.020	1.00	0.00030
Peas(117)	0.250	0.69	0.[illegible]0261
Peacnes(114)	10.[illegible]00	0.90	0.13490

MPI	TMRC	% ADI
7.5000 mg/day(60kg)	0.6261 mg/day(1.5kg)	8.35

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Unpublished,Tox Approved F1725,2143,2489,2599,2626,1E2493,2648,2653,2G[illegible]

2G2636

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Poultry(128)	0.40[illegible]	2.94	0.01766
Eggs(54)	0.200	2.77	0.00831
Celery(28)	3.000	0.29	0.01288
Lettuce(84)	10.000	1.31	0.19622
Filberts(58)	0.200	0.03	0.00009
Lettuce(84)	0.[illegible]00	1.31	0.00000
Sorghum(147)	5.000	0.03	0.00225
Sugar,cane&beet(154)	0. 50	3.64	0.00273
Sunflower(156)	1.000	0.03	0.00045
sugarcane (214)	2.000	0.[illegible]3	0. 0090

Artichokes(4)	0.200	0.03	0.00009
Corn,swe(9)	0.050	1.43	0.00107
Cherries(50)	10.000	0.10	0.01533
Barley(6)	8.000	0.03	0.00360
Wheat(170)	8.000	10.36	1.24354
Oranges(108)	2.000	2.17	0.06500
Grapefruit(65)	2.000	0.99	0.02974
Lemons(82)	2.000	0.17	0.00521
Peas(117)	0.200	0.69	0.00261
Almonds(1)	0.200	0.03	0.00009
Eggplant(53)	1.000	0.03	0.00045
Peppers(120)	1.000	0.12	0.00184

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NPI	TMRC	% ADI
7.5000 mg/day(60kg)	2.2362 mg/day(1.5kg)	29.82

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Current Action 3H5383

CROP	Tolerance	Food Factor	mg/day(1.5kg)
All foods(197)	0.050	100.00	0.07500

NPI	TMRC	% ADI
7.5000 mg/day(60kg)	2.3112 mg/day(1.5kg)	30.82

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DRAFT

The formulation on which all 5 acute toxicity studies were conducted is as follows:

0.50% Pyrethrins
1.00% Piperonyl butoxide
1.00% MGK-264
0.32% Fenvalerate

CBI removed

It is noted here that although the percentages of the constituents in the formulations proposed for registration varied slightly from that which was actually tested the differences were judged to be negligible and the data acceptable to support the registration of the products.

The registrant has also submitted references and supporting documents for the clearances of all the following ingredients as food additives:

Pyrethrins under 21 CFR 193.390.
Piperonyl butoxide, technical under 21 CFR 193.325.
MGK-264 under 21 CFR 193.324.

Description of specifications of [redacted]

An indirect food additive tolerance for fenvalerate (all foods is the crop category on the computer printout) would increase the percent of the ADI utilized from 29.82% to 30.82% and raise the TMRC from 2.2362 mg/day to 2.3112 mg/day.

Recommendations:

Toxicology Branch (TB) has no objections to the registration of these products provided the following conditions are met or agreed to:

- Residue Chemistry Branch raises no prohibitive objections and confirms the clearances of the listed ingredients as food additives.

- The petitioner adds the following statement to the precautionary labeling:

Inert ingredient information may be entitled to confidential treatment

Avoid contact with skin or clothing.

Additionally, the following statements should appear as statements of practical treatment, If on skin: Wash with plenty of soap and water. Get medical attention if irritation persists.

The data which can support the active ingredient, fenvalerate, in this formulation is attached. The data base for fenvalerate is nearly complete needing only the review of the currently submitted six (6) month dog study.

The data which can support the product labeling has been reviewed and is also attached.

Albin B. Kocialski

Albin B. Kocialski, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attachments:

OPP:HED:TOX:A.KOCIALSKI:sb 3/8/83 X77395 Rm 820 #m24

1. Summary of selected toxicology data considered in setting the tolerance

DATA TECHNICAL 07359

AOLD50 - Rat,	1-3 gms/kg (water vehicle) 450 mg/kg (DMSO vehicle)
90-Day rat feeding study	NOEL: 125 ppm
90-Day dog feeding study	NOEL: 500 ppm (highest dose tested)
18-Month mouse feeding study (ddy strain)	NOEL: less than 100 ppm with no onc effects at 3000 ppm the highest leve fed.
2-Year mouse feeding study (B6C3F1 strain)	NOEL: 10-50 ppm males and 50-250 ppm females. No oncogenic effects were noted at 1250 ppm the highest dose tested.
24-Month rat feeding study [CRL: COBS CD (SD) Br^4] strain	Not oncogenic at 1000 ppm - only level tested. Significantly decreased body weights at this dose level.
24-Month rat feeding study [CRL: COBS CD (SD) Br^4] strain	NOEL: 250 ppm (highest level fed; no oncogenic effects)
3-Generation rat reproduction study	NOEL: 250 ppm (highest level fed)
Teratology study: mice	Negative at 50 mg/kg/day (highest dose tested)
Teratology study: rabbits	Negative at 50 mg/kg/day (highest dose tested)

Mutagenicity Studies

a) Mouse dominant lethal - negative at 100 mg/kg/bw (highest level fed)

b) Mouse host mediated bioassay - negative at 50 mg/kg/bw (highest level fed)

c) Ames (in vitro) - negative

d) Bone marrow cytogenic study in the Chinese hamster - negative at 25 mg/kg/bw.

Studies Assessing Neurological Effects:

a) Hen study negative at 1.0 gm/kg/bw for five days; repeated again at 21 days.

b) Rat acute (8 day study) NOEL: 200 mg/kg/bw

c) Rat subchronic feeding study NOEL: 500 ppm (systemic)
(15-month rat feeding study) NOEL: 1500 ppm with respect to nerve damage

Subject: Acute Oral Toxicity LD50 - Rats

Test Compound: 0.50% Pyrethrins
1.00% Piperonyl butoxide
1.00% MGK-264
0.32% Fenvalerate

CONFIDENTIAL

CONFIDENTIAL

CBI removed

(also known as TL 2286)

Accession Number: 244289

Testing Facility: Biosearch Incorporated
Philadelphia, Pennsylvania

Project Number: 81-2516A

Study Period: May 27, - June 17, 1981

Report Submitted to Sponsor: August 19, 1981

Materials and Methods:

Five groups of ten (5 male and 5 female) Sherman-Wistar strain albino rats, weighing between 200 and 300 grams were gavaged at the following dose levels:

Group Number	Dose (gm/kg)
1	1.0
2	2.0
3	4.0
4	8.0
5	16.0

Animals were deprived of food overnite but not water.

Following administration of the test compound the animals were allowed food and water ad libitum during the 14 day observation period.

The animals were housed and maintained in compliance with the Animal Welfare Act (Pub. L-94-279) 9 CFR Part 3.

Results:

No animals died on the study. No unusual behavioral signs were observed at 4.0 gm/kg and below. Animals receiving 8.0 gms/kg were reported as slightly ruffled after 3-4 hours and essentially normal within 24 hours. Animals receiving 16.0 gms/kg were slightly ruffled and lethargic after 3-4 hours and much improved after 24 hours. Animals appeared essentially normal within 48 hours.

It was reported that gross pathologic examination revealed nothing remarkable for either sex.

Conclusion:

The AOLD50 is greater than 16.0 gms/kg.

Category of Toxicity: Category 4

Classification: Core - Guideline

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Subject: Acute Dermal Toxicity LD50 - Rabbits

Test Compound: TL-2286 (see AOLD50 study for break down of each constituent of the formulation)

Accession Number: 244289

Testing Facility: Biosearch Incorporated
Philadelphia, Pennsylvania

Project Number: 81-2516A

Testing Period: May 27, - June 25, 1981

Report Submitted to Sponsor: August 19, 1981

Materials and Methods:

Four groups of eight (4 male and 4 female) albino rabbits weighing between 2.0 and 3.0 kg were housed and maintained in compliance with the Animal Welfare Act (Pub. L-94-279) 9 CFR Part 3. All animals had their backs clipped free of hair 24 hours prior to testing. One-half of the animals in each sex/group had their backs abraded immediately prior to dosing. Each group received one of the following dose levels of formulated product, 4.0, 8.0, 16.0 or 20.0 gms/kg. Treated areas were covered with large gauze patches. An impervious material was then wrapped around the trunk of each animal. No controls were used in this experiment. The dressings were removed 24 hours post-dosing and excess material removed. Animals were then observed for 14 days. Gross autopsies were performed on all animals dying intercurrently and sacrificed at termination.

Results:

No animals died at dose levels of 16.0 gms/kg or lower. One male (unabraded skin) and one female (unabraded skin) died on days 4 and 6 respectively of the experiment. No visible toxic signs preceded either death. No unusual behavioral signs were noted at a dose level of 8.0 gms/kg or less. Animals receiving a dose of 16.0 gms/kg appeared slightly lethargic at 24 hours and appeared normal within 72 hours. Animals receiving 20.0 gms/kg appeared slightly lethargic after 24 hours and essentially normal within 72 hours. It was reported that gross pathologic examination revealed nothing remarkable.

It was also reported that moderate skin irritation was evident and persisted for 4-5 days at all dosage levels employed.

Conclusion:

The acute dermal LD50 is greater than 20.0 gms/kg.

Category of Toxicity: Category 4

Classification: Core - Guideline

CONFIDENTIAL

Subject: Primary Eye Irritation - Rabbits

CONFIDENTIAL

Test Compound: 0.50% Pyrethrins
1.00% Piperonyl butoxide
1.00% MGK-264
0.32% Fenvalerate

CBI removed

(also known as TL-2286)

Accession Number: 244289

Testing Facility: Biosearch Incorporated
Philadelphia, Pennsylvania

Project Number: 81-2516A

Testing Period: May 26 - June 2, 1981

Report Submitted to Sponsor: August 19, 1981

Materials and Methods:

Six healthly young adult albino rabbits were employed in this study. A volume of 0.1 ml of the experimental material was instilled into the right eyes of the test animals while the other eyes remained untreated and served as controls. The test material was not washed from the eyes.

The treated eyes were examined at 1, 2, 3, 5 and 7 days following instillation of the test material. Eyes were scored using the method of Draize.

All animals were housed and maintained in compliance with the Animal Welfare Act (Pub. L-94-279) 9 CFR Part 3.

Results:

Eye irritation was not observed.

Conclusion:

The formulation is not an eye irritant under the test conditions.

Category of Toxicity: Category 4

Classification: Core - Guideline

Subject: Primary Skin Irritation - Rabbits

Test Compound: TL-2286 (see acute oral study for formulation composition)

Accession Number: 244289

Testing Facility: Biosearch Incorporated
Philadelphia, Pennsylvania

Project Number: 81-2516A

Testing Period: May 26, - May 29, 1981

Report Submitted to Sponsor: August 19, 1981

Materials and Methods:

One group of 6 albino rabbits was clipped free of hair over a wide area. One site was abraded sufficiently deep to penetrate the stratum corneum but not the dermal layer. The skin at the second site was allowed to remain intact.

A 0.5 ml portion of test material was applied to the abraded and unabraded site on the same rabbit. Gauze patches were then placed over the treated areas and an impervious material was wrapped snugly around the trunks of the animals to hold the patches in place.

The wrapping was removed at the end of the 24 hours period and the treated areas examined. A second reading was recorded at 72 hours. The Draize method of scoring was employed.

All animals were housed and maintained in compliance with the Animal Welfare Act (Pub. L-94-279) 9 CFR Part 3.

Results:

The primary irritation score was calculated to be 3.0.

The maximum possible score is 8.

Conclusion:

The formulation is considered to be a moderate irritant under the test conditions.

Category of Toxicity: Category 3

Classification: Core - Guideline

Subject: Acute Inhalation Toxicity - Rats

Test Compound: TL-2286 (see complete break down of individual constituents with the AOLD50 study)

Accession Number: 244289

Testing Facility: Biosearch Incorporated
Philadelphia, Pennsylvania

Project Number: 81-2516A

Testing Period: May 28, - June 11, 1981

Report Submitted to Sponsor: August 19, 1981

Materials and Methods:

One group of 5 male and 5 female albino rats was used in this study. No control animals were employed. All animals were housed and maintained in compliance with the Animal Welfare Act (Pub. L-94-279) 9 CFR Part 3.

Animals were exposed to the test material in a 260 liter plexiglass exposure chamber for one hour. The material was administered as an aerosol which was generated by a six jet collision nebulizer. The air was passed thru a dessicant prior to being passed through the test material. The rate of flow through the chamber was 20.0 liters per minute at a temperature of 70°F.

The average concentration of the aerosol over the one hour exposure period was calculated to be 14.5 mg/liter by differential weighing of the flask from which the aerosol was generated. This was the maximum concentration which could be attained. Particle size of the aerosol was determined using an Andersen Sampler cascade impactor, with the sample of air taken from the breathing zone of the animals. The amount of aerosol impacting on each plate of the Andersen Sampler was determined by differential weighing. The mass median diameter of the aerosol was calculated to be 0.84 u (microns).

Following exposure the animals were observed for a 14 day period.

Animals were sacrificed at 14 days and a gross pathological examination conducted.

Results:

It was reported that no aniamls died during the 14 day observation period.

No adverse signs were noted during the one hour exposure and no untoward signs were observed during the two week post-exposure observation period.

A gross pathologic examination revealed no remarkable findings.

Conclusion:

The AILC50 for the formulation is greater than 14.5 mg/l (maximum attainable concentration).

Category of Toxicity: Category 4

Classification: Core - Guideline

Subject: Guinea Pig Contact Dermal Irritation/Sensitization 07359
Modified Buehler Method.

Test Compound: TL-2286 (see AOLD 50 study for formula composition).

Accession Number: 244289

Testing Facility: Biosearch Inc.

Project Number: 81-2516A

Test Period: June 8 - July 15, 1981

Report Submitted to Sponsor: August 19, 1981

Materials and Methods:

One group of 10 male albino guinea pigs weighing between 300 and 400 grams each was employed in this study. All animals were housed and maintained in compliance with the Animal Welfare Act (Pub. L-94-279) 9 CFR Part 3.

A volume of 0.5 mls of material was applied to the intact skin (shaved skin assumed) of the animals. A gauze patch was placed over the treated area and an impervious material was wrapped snugly around the trunks of the animals to hold the patch in place. After a 24 hour contact period, the patch was removed and the animals were allowed to rest for one day. Following this rest period, another application was made to the same skin site using a fresh sample. This procedure was repeated for a total of ten applications, after which time the animals were rested for a two week period. At the end of the two week period a challenge application was put on the skin at a site removed from the original locus. The challenge application remained on the skin for 24 hours.

Twenty-four hours after each induction stage application and 24 and 48 hours after the challenge application, the sites were examined for irritation and reaction using the Draize method of scoring.

Results:

A barely perceptible (score = 1) erythema but no edema was observed in all animals receiving the first 10 administered doses.

The challenge dose elicited a positive response for erythema (score = 1) in 4 animals at the 24 hour reading which continued to manifest itself in 3 of the animals at the 48 hour reading (score = 1). Edema was not observed at any post-challenge period.

Conclusions:

Based upon the results of the study it was concluded that:

- the material does not appear to be a primary skin irritant,
- does not appear to be a sensitizing agent,
- the material appears to cause skin fatigue.

Category of Toxicity: Non-Sensitizing

Classification: Core - Guideline